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Health is a precious and most valuable possession that has been considered as the second blessing, and vital principles of bliss. Without health life is considered no life, and all our happiness lies in health. People all over the world have realized the importance of health and the following proverbs of different languages highlight the importance given to health: Health is wealth (Kannada); Health is better than wealth (English); From bitterness of disease man learns the sweetness of health (Spanish); Good health or bad makes our philosophy (French); Every healthy man is king (Gaelic); Wealth without health is half sickness (Italian); One can always be healthy as long as one is not ill (Russian).

Benjamin Disraeli had said 'the health of people is really the foundation upon which all their power as a State depend'. World Health Organization (WHO) has given the slogan 'Invest in health, build a safe future' for WHO Day on 7<sup>th</sup> April 2007. The slogan addresses to one of the most vital concerns of the current times. Globalization and rapid travel surpassing the international time-zones have enabled the easy spread of the new and existing diseases beyond the national borders and have affected the collective security.

Avian influenza and severe acute respiratory syndrome (SARS) have spread from one country and region to the next. Avian influenza (flu) epidemic swept across South Korea, Japan, Taiwan, Vietnam, Thailand, Cambodia, Laos,

Indonesia, China and Pakistan during 2006. This is an infectious disease caused by a highly contagious virus. The disease appears to have jumped the species barrier, infecting human and causing death. It necessitated culling of millions of chicken, ducks, geese and other birds to prevent the spread of the disease. The public health authorities were put on high alert to prevent the occurrence of a pandemic in human beings. The speed at which this virus spread was unprecedented.

There is a risk that humans could become infected with both the avian and human influenza virus at the same time. Avian flu virus could swap genetic material with human flu to produce a highly contagious mutant. The parts of Asia affected by the outbreak of avian flu were put on strict measures of isolation and culling of millions of chicken infected with a strain of bird flu and isolation of persons thought to be infected. The 2006 outbreak affected every country contiguous either by land or sea. The entry of any poultry products were not allowed from those regions. The presence of antibodies against H5N1 virus was tested. The country should be vigilant about persons entering the country who appear to be presenting features of flu-like illness.

A mysterious form of highly contagious pneumonia was reported in Guangdong Province of People's Republic of China in later part of 2002 and subsequently spread to parts of South-east Asia during the early months of 2003. The illness has

been referred to as SARS. The disease causes flu-like symptoms initially, rapidly to be followed by respiratory problems, often serious leading to higher mortality.

SARS is a highly infectious disease caused by a corona virus. It is transmitted by close contact with aerosolized droplets and bodily secretions from an infected person. It causes diffuse alveolar damage. The person exhibits fever, cough, shortness of breath and difficult breathing. There should be history of a close contact with a person who was known to have suffered from SARS within the past 10 days or travel within past 10 days of onset of symptoms to places which have reported cases of the disease. Prevention of SARS involves avoidance of close contact with SARS patients. Persons suspected of having SARS must be isolated and should limit their interactions outside hospital settings. Quarantine of patients before they spread disease, quarantine or close monitoring of all the people they have come into contact with and a clampdown of social gatherings and travel are important.

HIV/AIDS since 25 years has been racing across nations, adversely impacting their economics and threatening their stability. New diseases have appeared and old ones have re-emerged as epidemic/pandemic prone diseases to present an acute threat to life. Climate change, natural disasters, chemical and nuclear accidents and bioterrorism also hold the potential to threaten international public health

security.

Global warming is occurring at an alarming speed due to combustion of fossil fuels. It is associated with anthropogenic emission of greenhouse gases, air-borne particulates, nitrogen and sulphur dioxide. Global warming having health impact has emerged as a public health challenge. Global warming associated with rainfall, humidity, water-logging, active photosynthesis of vegetation, is changing the ecology of many arthropod vectors transmitting diseases to human beings. Warmer temperatures increase mosquito and tick vector overproduction, biting and transmission of disease such as malaria, Rift Valley fever, and Lyme disease. Dengue fever and Chikungunya fever spread by the mosquito, *Aedes aegypti*, have widened their geographical boundaries in tropical regions. The spread and activities of the sandflies, vectors of Leishmaniasis, is strongly influenced by ambient temperature. There is an explosion of the mouse population following heavy rainfall and they may increase the chances of outbreak of Hantavirus pulmonary syndrome.

The climate change in the coming years threatens human population with health hazards by disrupting water and food supplies, and increased spread of vector-borne diseases. It has called for reduction of green house gas emissions by reducing combustion of fossil fuels, development of renewable energy technology, establishment of stations equipped with remote sensing and geographic information system to monitor sea-level rise and extreme weather conditions.

The dissemination of anthrax spores through US mails and the resultant cutaneous and inhalation anthrax led to

a campaign for preparedness against bioterrorism. Bioterrorism refers to the use of chemical or biological weapons for terrorism. Though the morbidity and mortality caused by bioterrorism have been very small compared to that produced by the use of other weapons, there is need for preparedness against any possible bioterrorism.

Natural disasters such as earthquake, floods, cyclone, tsunami, and famine strike the globe frequently. WHO has defined disaster as 'any occurrence that causes damage, economic disruption, loss of human life and deterioration in health services on a scale sufficient to warrant an extraordinary response from outside the affected community or area'. There is ecologic disruption which exceeds the capability of the affected community to make adjustments. The rescue and relief faces many difficulties. In addition to medical relief, quick removal and disposal of corpses, restoration of water supply, food and maintenance of sanitation are important to prevent widespread epidemics. The casualties are to be evacuated from the site as fast as possible to a place where proper treatment can be given on priority basis.

William Mayo once said, 'of all cooperative enterprises public health is the most important and gives the greatest returns'. Hence there is need for investment in health. Health emergencies cause global concerns and an effective response requires international cooperation. This has been amply exhibited by different nations following tsunami disaster and outbreak of SARS. The WHO slogan highlights the vital need to invest in human resources and strengthen the health systems to enable the international community to effectively meet the public health risks

and challenges. WHO is assisting the countries to strengthen their public health risks and challenges.

The revised and broadened international health regulations 2005 are coming into effect in June 2007 to provide support to the countries to stabilize global health. Under this international agreement the member states of WHO are obliged to prevent and control the spread of disease inside and outside their borders. They have to maintain core surveillance and exhibit their capabilities to detect, assess, notify and report public health events to WHO and to respond to public health risks and public health emergencies. All must keep in their mind about the closing phrase found in many Latin letters: 'cura ut valeas' (Guard your health).

### Ancient Greece

While surgeons are now considered to be specialised physicians, the profession of surgeon and that of physician had different historical roots. For example, Greek tradition was against opening the body, and the Hippocratic Oath warns physicians against the practice of surgery. Specifically, *cutting persons laboring under the stone* (i.e. lithotomy, an operation to relieve kidney stones) was to be left to *such persons as practice [it]*. Of course, most knowledge of surgery comes from dissecting bodies, a science which was repulsive to many healers.

# Drug-Resistant Tuberculosis

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Commentary

**M**ulti-drug resistant (MDR) tuberculosis (TB) is being increasingly recognized in the recent years all over the world. The term refers to the disease due to *M. tuberculosis* that is resistant to the two most effective current anti-tuberculosis drugs, isoniazid and rifampicin with or without resistance to other drugs (poly-resistance)<sup>1</sup>. It is an iatrogenic problem. Extensively (Extremely) drug-resistant (XDR) tuberculosis is caused by a strain of *Mycobacterium tuberculosis* resistant to isoniazid and rifampicin (as in MDR-TB) in addition to any fluoroquinolones and at least one of the three injectable drugs such as capreomycin, kanamycin and amikacin<sup>2</sup>.

## Multi-drug resistant tuberculosis

After dramatic outbreaks of multi-drug-resistant tuberculosis in the early 1990s, resistance became recognized as a global problem. MDR-tuberculosis (TB) now threatens the inhabitants of the countries in Asia, Africa, Europe and the Americas. A new research finding from South Africa on an extensively drug-resistant strain of *M. tuberculosis* that causes tuberculosis is alarming the experts<sup>3</sup>. The new strains of multi-drug resistant-, and extremely drug-resistant strains of tubercle bacilli have emerged despite availability of effective anti-tuberculosis, and it is due to their ineffective administration. They have great significance for the public health field. The causes of drug resistance are many (Table-1)<sup>4</sup>.

**Table -1, Causes of resistance**

Poor adherence to treatment
Prescription of inappropriate combinations of drugs
Prescription of inadequate dosage of drugs
Inappropriate rhythm of administration
Use of unreliable combinations
Addition of another drug to a failing regimen
Erratic drug supply
Malabsorption of properly prescribed drugs

Drug resistance has to be suspected in a patient who continues to remain sputum-positive after four months of regular treatment with an established short-course chemotherapy regimen. A history of anti-tuberculosis treatment predicts the occurrence of MDR-TB. Non-compliance with the anti-tuberculosis drugs therapy, and HIV-infection aggravate the situation.

## Extensively drug resistant tuberculosis

Looking at the emergence of extremely drug resistant strains of tuberculosis bacilli, the World Health Organization (WHO) has expressed concern and has called for urgent measures to strengthen and to implement effectively the prevention of the global spread of the deadly strains of tuberculosis. The newly identified strains of XDR strains of tubercle bacilli leaves the patients,

including those living with human-immunodeficiency virus (HIV), virtually untreatable with the currently available anti-tuberculosis drugs, and death becomes imminent.

The description of XDR-TB was first given in early 2006 following a joint survey by World Health Organization (WHO) and the US Centres for Disease Control and Prevention (CDC). Resistance to anti-tuberculosis drugs is a reflection of poorly managed tuberculosis. The care-giver, patient and drugs play a part in the emergence of drug-resistant strains. The reasons include incorrect drug prescribing practices by the care-giver, poor quality of drugs or erratic supply of drugs, and patient non-adherence.

## Epidemiology of XDR-TB

The findings from a survey carried out by WHO and CDC on data from 2000 to 2004 has shown that XDR-TB is encountered in at least 17 countries of the World. However its occurrence was more frequent in the countries of former Soviet Union and Asia<sup>5</sup>.

The survey has shown that in United States, 4% of isolates of MDR-TB met the criteria for XDR-TB. 15% of isolates of MDR tuberculosis in the Republic of Korea were XDR strains. In Latvia, a country with one of the highest rates of MDR-TB, 19% of MDR-TB cases met the criteria for XDR-TB (5). The data on the recent outbreak of XDR-TB in an HIV-positive population in KwaZulu-Natal, a province of South Africa has shown

alarmingly high rates of rapid death. Of the 544 patients studied at a rural hospital, 221 had MDR-TB. Of them 53 were defined as XDR-TB. Among them 44 had been tested for HIV and all of them were HIV-positive. 52 of 53 patients died of tuberculosis on an average, within 25 days including those getting benefit from anti-retroviral therapy<sup>6</sup>.

Scarce drug-resistance data is available from Africa. While population prevalence of drug-resistant TB appears to be low compared to Eastern Europe and Asia, drug-resistance in the region is on the rise. Given the underlying HIV epidemic, drug-resistant tuberculosis could have a severe impact on mortality in Africa and other countries and it requires an urgent preventive action.

### Immune defense mechanism

There is an increased resistance to re-infection in persons infected with tubercle bacilli either naturally from virulent strains of *M tuberculosis* or artificially following vaccination with attenuated, live tubercle bacilli. In addition, those infected develop a delayed hypersensitivity to tuberculo-protein. These two changes-acquired resistance (tuberculo-immunity) and tuberculin hypersensitivity-are specific immunological reactions and are cell-mediated. These responses are acquired and develop only after the specific antigenic stimulus. They play a key role in the pathogenesis of tuberculosis<sup>7</sup>.

Lenzini and co-workers have established a spectrum of progressive human tuberculosis on a clinical and immunologic basis.<sup>8</sup> The patients are categorized into four groups: one polar group exhibits fully active cell-mediated reactivity and the other un-reactive

polar group that does not demonstrate any cell-mediated immunity. Between them are two intermediate groups, leaning towards the reactive group and another one leaning towards the un-reactive group. There is predominance of lymphocytes and epitheloid cells to the reactive group. The number of tubercle bacilli in the tissues and the level of antibodies increase towards the un-reactive group and there is rapid spread of bacilli and lesions in the lungs and other organs<sup>8</sup>.

The studies on the immune defenses of people with tuberculosis have shown that the problem is not so much of an inability of the body's defenses to deal with the organism but abnormally-regulated defense mechanisms. Thus, in active tuberculosis, the immune responses rather than attacking the tubercle bacilli, cause gross tissue destruction with the formation of huge cavities in the lung as well as causing systemic manifestations such as fever and wasting.

Masjedi and co-workers from Iran obtained sputum specimens from a total of 2030 patients with tuberculosis and digested, examined microscopically for presence of acid-fast bacilli and then inoculated into Lowenstein-Jensen slants by standard procedure<sup>9</sup>. Testing of susceptibility to first-line anti-tuberculosis drugs was performed for 1284 isolates of *M. tuberculosis*. Subsequently, the strains that were identified as multi-drug resistant *M tuberculosis* (113 isolates) were subjected to susceptibility testing for second-line drugs. Spot-ligotyping and restriction fragment-length polymorphism were performed for strains that were identified as XDR-*M tuberculosis*.

A total of 12 (10.9%) of 113 multi-drug resistant *M tuberculosis* strains were

resistant to all 8 second-line drugs tested and therefore, were denoted as XDR *M tuberculosis*. Retrospective analysis of the cases of XDR-TB showed that all of them belonged to 1 of 2 epidemiological clusters, either a single-family cluster (4 cases) or a cluster of close contacts (8 cases). The strains were identified as belonging to the *M tuberculosis* super-families Haarlem I and East African Indian.

### Management

Early, accurate diagnosis and institution of effective treatment properly under supervision for a proper duration are essential in the control of tuberculosis. The treatment of patients whose organisms are resistant to the standard anti-mycobacterial agents poses many difficulties. The tubercle bacilli and their progeny remain viable and multiply in the presence of anti-mycobacterial agents in a concentration that would normally destroy or inhibit their growth. Inadequate treatment select out drug-resistant strains which then proliferate. Further inadequate and improper treatment maintains the vicious cycle leading to emergence of strains that are resistant to other drugs until creation of MDR and later XDR tuberculosis. Drug resistance poses a serious limitation to the successful treatment and control of tuberculosis.

There is decreased clinical response, persistence of acid-fast bacilli in the sputum, and radiological deterioration even after continuous therapy for six months. These are indications that the infecting organisms are resistant to the drugs used in the treatment. Inappropriate use of second-line anti-tuberculosis drugs in a patient for whom first-line drugs are failing ends in XDR-TB. The patient then spreads the infection

to individuals in close contact who acquires primary XDR-TB.

XDR-TB poses a grave public health threat, especially in populations with high rates of HIV infection and where there are few health care resources. Treatment regimens for drug-resistant tuberculosis are less effective, more expensive and prolonged. Further the patient having drug resistant tuberculosis poses public health danger of spread of resistant organisms.

The efficacy of treatment of resistant cases-both of MDR and XDR-TB- is worse than that of the original treatment. Hence, the initial intensive treatment with proper chemotherapy has vital importance. Initial intensive treatment reduces the total bacterial population to such a low number that the risk of the emergence of resistant strains becomes insignificant. The loss of sensitivity of tubercle bacilli to standard drugs is an undesirable and harmful phenomenon.

Drug resistance has to be suspected in a patient who continues to remain sputum positive after four months of regular treatment with an established short-course chemotherapy regimen. A history of improper and inadequate anti-tuberculosis treatment predicts the occurrence of MDR-TB and of XDR-TB. Non-compliance with the therapy, and HIV-infection aggravate the situation.

The treatment of MDR-TB and of XDR-TB poses many challenges to the treating physician. The treatment is less effective, more toxic and expensive. A detailed history of previous treatment for tuberculosis has to be obtained. It should include the names of drugs-both first-line and second-line-the dosage, duration and regularity of intake. Drug susceptibility testing is necessary to ensure that patients

receive a quick diagnosis and properly selected drugs for adequate duration. It will facilitate to interruption of transmission of drug-resistant organisms.

### WHO guidelines

WHO Guidelines for the Programmatic management of drug resistant tuberculosis include the following:

- strengthen basic TB care to prevent the emergence of drug-resistance
- ensure prompt diagnosis and treatment of drug resistant cases to cure existing cases and prevent further transmission
- increase collaboration between HIV and TB control programs to provide necessary prevention and care to co-infected patients, and
- increase investment in laboratory infrastructure to enable better detection and management of resistant cases.

The patient with MDR-TB should be given at least four drugs which he/she has not received in the past or to which the bacilli have demonstrated susceptibility by laboratory testing<sup>11</sup>. The chance of receiving at least two drugs having *in vitro* activity against tubercle bacilli are greater if greater number of drugs, usually six or seven are used in the treatment. However use of more number of drugs is associated with greater toxicity, drug-drug interactions and expense. The treatment of XDR-TB poses further problems as the organisms are resistant to most of second-line of anti-tuberculosis drugs. The patients have to receive individually tailored regimens containing at least four drugs which they had not received previously or to which they were known to be susceptible. Second-line anti-tuberculosis drugs must

be administered for at least 18 months under strict monitoring supervision.

### Increasing threat

XDR-TB presents an increasing threat to global tuberculosis control. XDR-TB has main implications for the management of patients with HIV and for HIV control. High prevalence of HIV predicts extreme vulnerability to tuberculosis. Most crucial management issues in XDR-TB treatment remain unanswered. Emergence of drug resistance is prevented by identifying cases of drug-susceptible disease and treating them with well tested regimens in a proper dosage for a proper duration. It has to be ensured that the patient completes full course of treatment till cured. There is need to treat patients with established MDR-TB with a complicated regimen including second-line drugs, and followed for a longer duration to prevent relapses and emergence of XDR-TB. Antiretroviral drugs protect against tuberculosis by restoring patients' immuno-competence.

### Conclusion

Retrospective cohort studies have shown the emerging threat of extremely drug resistant tuberculosis. Such a condition requires an aggressive treatment regimen and high-end dosing of drugs. The second-line drugs have low potency and increased toxicity. The treatment has to be carried out under direct observation to achieve compliance. High cost of treatment puts great hurdle in resource-poor settings. Emergence of CDR-TB reflects a failure to implement the measures recommended in the WHO's Stop TB Strategy<sup>11</sup>. The strategy emphasizes the extensive use of DOTS program, addressing HIV-associated tuberculosis and drug resistance strengthening health care system and primary core services. Opportunities to

treat XDR-TB in developing countries has been made possible through Global fund to fight AIDS, TB and malaria, and the Green Light committee for access to second-line anti-tuberculosis drugs. More studies are needed to guide clinicians in the management of this emerging problem.

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### History of Surgery at Mayo Clinic

Surgery at Mayo Clinic began with the frontier practice of Dr. William Worrall Mayo. Dr. Mayo's two sons, William J. and Charles H., assisted him in his practice at very early ages. Saint Marys Hospital opened in Rochester on Sept. 30, 1889 & Dr. Charlie removed a cancerous tumor of the eye, his first surgery, assisted by his brother and father. Between 1889 and 1905, the Mayos did all operations at Saint Marys Hospital, themselves. To handle the growth of their practice, the Mayos opened a third operating room at Saint Marys in 1905.

The Mayos maintained an "open-door" policy to other members of the medical profession. During operations, the brothers always discussed their procedures for the benefit of visitors. Over the operating tables, large adjustable mirrors provided a complete view of the operating field. This demand for advanced medical training led the

Mayos to establish the country's first graduate program in clinical medicine in 1915.

Each physician devoted attention to a particular area of medicine, and all physicians combined skills to provide superior patient care. This specialization led to the development of new surgical disciplines, including: orthopedics, neurosurgery, ophthalmology, thoracic surgery, dental surgery and more. The Mayo brothers routinely visited other medical centers around the world to learn more about new procedures and ideas. They brought their findings back to Rochester to implement. This practice sparked a habit of innovation at Mayo. For example, early Mayo surgical contributions include the development of the low anterior resection for colon and rectal cancer, endoscopic injection of esophageal varices, and advances in resection of the stomach for cancer. In addition, many operating techniques and instruments still in use today were developed by Mayo Clinic surgeons, including the Balfour retractor, the Mayo stand, the Mayo scissors, the Adson pickups, the Harrington Behrens, and the Adson-Beckman retractors. Mayo Clinic history includes more than a century of innovations in the surgical treatment of patients, from the first open-heart surgery in 1955 to the first total hip replacement in 1969 to the early use of robotic laparoscopic surgery in 2002. Today, 255 Mayo Clinic surgeons treat more than 76,000 surgical patients each year, proving that the Mayo legacy of surgical teamwork and innovation is still alive.

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About 70% of newly detected cases are exophytic papillary tumors confined largely to the mucosa (Ta) (70%) or less often to the submucosa (T1) (30%). These tumors tend to be friable and have a high propensity for bleeding. Their natural history is characterized by a tendency to recur in the same portion or another part of the bladder over time (a phenomenon termed “polychronotropism”) and these recurrences can be either at the same stage as the initial tumor or at a more advanced stage. Papillary tumors confined to the mucosa or submucosa are generally managed endoscopically by complete resection. Progression to a more advanced stage may result in local symptoms or, less commonly, symptoms related to metastatic disease. It is estimated that 10% to 70% of patients with a tumor confined to the mucosa will have a recurrence or a new occurrence of urothelial (transitional cell) carcinoma within 5 years. These probabilities of progression vary as a function of the initial stage and grade. Refining these estimates for the individual patient is an area of active research.

### Staging and grading

The most commonly utilized staging system is the tumor, node, metastasis (TNM) system, as shown in. Bladder carcinomas are graded as well differentiated (G1), moderately differentiated (G2), poorly differentiated or undifferentiated (G3-4). However, the determination of grade

has a greater impact on the management of noninvasive tumors because most muscle-invasive tumors (ie, greater than T1) are G3. An alternative grading system of low or high grade has been proposed, and it is our intent to transition to this classification system over the next three years. We will retain the present classification system for now since it is commonly used by practicing urologists. A comparison of the different classification systems is presented in the Principles of Pathology Management.

Papillomas are considered to be benign tumors that closely resemble the normal urothelium. Grade 1 papillary carcinoma in contrast can be recognized histologically because they have more than the normal seven epithelial layers, normal polarity of the nuclei, and minimal pleomorphism. Papillomas and G1, Ta carcinomas are managed almost exclusively by endoscopic means because they generally do not progress to a higher, more lethal stage. In contrast, Ta, G3 tumors have a much higher chance of progression to a more advanced stage.

Once stage and grade have been determined, treatment decisions are based on the depth of invasion and extent of disease. The treatment of bladder cancer entails the disciplines of urologic surgical oncology, radiation oncology, and medical oncology. For many of the complex strategies the involvement of multidisciplinary teams will optimize results. The general principles for surgery, chemotherapy and radiation therapy are explained on respectively.

Non muscle-invasive tumors are divided into noninvasive papillomas or carcinomas (Ta), those invading the lamina propria (T1), and CIS. These tumors have previously been referred to as “superficial” tumors, an imprecise term which should be avoided. In some cases, a papillary or T1 lesion will be documented as having an associated in situ component (Tis). The standard treatment in such cases is the repeat of TUR. However, depending on the depth of invasion and grade, intravesical therapy may be recommended. This suggestion is based on the estimated probability of recurrence (ie, a new tumor formation within the bladder) and progression to a more advanced, usually invasive stage - events that should be considered independently.

Cystectomy is rarely considered for a Ta, G1 or G2 lesion. Intravesical therapy is used in two general settings: as prophylactic or adjuvant therapy following a complete endoscopic resection or, rarely, as therapy aimed at eradicating residual disease that could not be completely resected. This distinction is important, as most published data reflect prophylactic or adjuvant use with the aim of preventing recurrence and/or delaying progression to a higher grade or stage. In many cases, intravesical therapy is given to patients who do not require it because the probability of recurrence or progression is low. Management of the different histologic subtypes of different grades is outlined below.

### Papilloma/Ta, G1 or G2

TUR without intravesical therapy is the standard treatment for Ta, G1 and Ta, G2 tumors. Since patients diagnosed with these tumors have a relatively high risk of recurrence, in addition to observation, the panel also offers consideration of a single dose of intravesicular chemotherapy (not immunotherapy) within 24 hours of resection. Close follow-up is needed, even though the risk of progression to a more advanced stage is low. As a result, these patients are advised to undergo a cystoscopy at 3 months initially, and then at increasing intervals. If no recurrences develop during the first year, the interval between evaluations can be increased. Patients in whom a recurrence is documented are treated with TURBT and adjuvant therapy based on the stage and grade of the recurrent lesion, and they are then followed at 3-month intervals. Intravesical therapy is recommended for patients who have a history of recurrences.

### **Ta, G3 disease**

Tumors staged as Ta, G3 lesions are considered to be high-grade papillary tumors with a relatively high risk of recurrence and progression towards more invasiveness. For this reason, in addition to observation, they are treated with intravesical *Bacillus Calmette-Guérin* (BCG) or mitomycin (MMC), in the same manner as T1, G1-2 tumors with BCG being the preferred option for post-operative treatment.

### **Tis**

Primary Tis is a high-grade lesion that is believed to be a precursor of invasive bladder cancer. Standard therapy for this lesion is a complete endoscopic resection followed by intravesical therapy with BCG. This is generally given once a week for 6 weeks, followed by a 4-6 week rest

period, with a full reevaluation at week 12 (ie, 3 months) after the start of therapy. Patients with Tis who have recurrent/persistent disease at the 12-week (3-month) evaluation can be given a second course of BCG or MMC induction therapy (no more than 2 consecutive courses). If a second course of BCG is given and there is residual disease at the second 12-week (3-month) follow-up, a cystectomy should be strongly considered. Depending upon prior treatment, the extent of the disease, and the frequency of recurrences, intravesical therapy with the different intravesical agent (mitomycin, or less commonly valrubicin, alpha-interferon, or BCG plus alpha-interferon) is an alternative to cystectomy. In some centers, however, these patients might still be candidates for investigational therapies. For patients with complete response at the follow-up cystoscopy, whether one or two courses of induction therapy were administered, maintenance therapy with BCG is advised, although this recommendation is not universal. Regardless of whether or not maintenance therapy is administered, patients with Tis should be followed at 3-month intervals with a urinary cytology and cystoscopy for the first 2 years, and if no recurrences are documented, every 6 months in the third and fourth years and then annually. Imaging of upper tract collecting system every 1 to 2 years is also recommended with or without urinary tumor markers (category 2B) in selected cases. If progression to an invasive lesion is documented at any point during follow-up, a radical cystectomy is recommended. Although controversial, patients who present with recurrent superficial tumors prior to the documentation of a muscle-invading lesion are generally not considered to be candidates for bladder-

sparing approaches.

### **T1 disease**

T1 lesions, those invading lamina propria, are considered to be potentially dangerous (usually T1G2 or G3) and have a high risk of both recurrence and progression. These tumors may occur as solitary lesions or as multifocal tumors, with or without an associated in situ component. They, too, are treated with a complete endoscopic resection followed by intravesical therapy (this is optional for G1 or G2 lesions). Within the category of T1 disease, two risk strata can be identified: low-risk (G1, G2, or solitary) and high-risk (G3 or multifocal lesions, tumors associated with vascular invasion, or lesions that recur after BCG treatment).

### **Low-risk disease**

After the initial TUR, patients with low-risk disease are observed or undergo intravesical treatment with BCG or mitomycin. Follow-up is similar to that previously outlined above for Ta, G1-2 disease, with a urinary cytology and cystoscopy recommended at 3-month intervals for the first 2 years, repeated at increasing intervals over the next 2 years, and annually thereafter. If cytology study is found positive despite the negative imaging and cystoscopy results, random biopsies including TUR and prostate biopsy in male patients are recommended. Recurrent disease is treated as appropriate for the stage documented at the time of relapse.

### **High-risk disease**

Patients with high-risk disease (T1, G3) can be treated with a course of BCG (preferred, category 1), mitomycin, or radical cystectomy after a certain and satisfied resection. If the complete resection is uncertain based on the tumor



size and location, no muscle is shown in the specimen, lymphovascular invasion, or inadequate staging is speculated, repeat resection of tumor or cystectomy followed by intravesical therapy with BCG (category 1) or mitomycin is recommended (). Evolving data suggest that the preferred approach may be early cystectomy if residual disease is found due to the high risk of progression to a more advanced stage. If high-risk disease is managed conservatively and does not respond to BCG, a cystectomy should be performed.

Before any treatment is advised, the following workup procedures are recommended to determine the clinical staging. Laboratory studies such as complete blood cell count (CBC) and chemistry profile including alkaline phosphate need to be done, and the patient should be assessed for the presence of regional and/or distant metastases. This evaluation should include a cystoscopy, EUA/TURBT, chest x-ray, bone scan in patients with symptoms or elevated alkaline phosphate, and evaluation of the upper tracts with a CT or MRI scan of the abdomen and pelvis. Some physicians advocate performing magnetic resonance imaging (MRI) to determine the depth of invasion within the bladder and, in particular, to ascertain whether a tumor has reached the perivesical fat (T3b). Unfortunately, CT scans, ultrasound, or MRI cannot accurately predict the true depth of invasion.

### **Organ-confined disease (T2a, T2b)**

Surgical treatment with radical cystectomy is still the most effective local therapy in muscle-invasive bladder cancer. Two critical issues exist in the management and prognosis of these patients: (1) whether or not a palpable

mass is appreciated at the time of the EUA, and (2) whether or not the tumor has extended through the bladder wall. Tumors that are organ-confined (T2) have a better prognosis than those that have extended through the bladder wall to the perivesical fat (T3) and beyond. Primary surgical treatment for T2 lesions include radical cystectomy with the consideration of neoadjuvant chemotherapy in selected patients, and segmental cystectomy only in patients with a single tumor (solitary lesion in a suitable location), and no any presence of CIS, nor previous multifocal bladder cancers. If no neoadjuvant chemotherapy was given, post-operative adjuvant chemotherapy is considered in those patients based on the pathologic risk such as positive nodes and pathologic T3 lesions. If segmental cystectomy had been performed, adjuvant RT or chemotherapy based on pathologic risk (positive nodes, positive margin, high-grade, and pathologic T3 lesions) should be considered. For patients with superficial muscle-invasive T2 disease and without hydronephrosis, bladder-sparing treatment (category 2B) with chemotherapy and radiation therapy may be possible following complete TURBT. In highly selected patients with extensive comorbid disease or poor performance status, chemotherapy as well as radiation therapy or TURBT is recommended. For those patients not undergoing cystectomy, evaluation with cystoscopy and tumor site re-biopsy is necessary after the primary treatment. Radical cystectomy is the standard treatment if tumor is found. Otherwise, observation, further consolidation chemotherapy with radiation, and/or adjuvant chemotherapy alone is recommended.

### **Relapses in the bladder after**

### **bladder-sparing approaches**

Treatment of relapses is based on the extent of disease at the time of relapse, with consideration given to the prior treatment that a patient has received. Tis, Ta, or T1 tumors are generally managed with intravesical BCG therapy. If there is no response, a cystectomy is advised. A positive cytology with no evidence of disease in the bladder should prompt selective washings of the upper tracts and an evaluation of the prostatic urethra. If the selective cytologies are positive, patients are managed as described below under treatment of upper tract tumors. Invasive disease is generally managed by radical cystectomy and a second attempt at bladder preservation is not advisable. All patients who relapse after bladder-sparing therapy and are being considered for radical cystectomy should be evaluated for medical comorbidities and undergo a full restaging evaluation to ensure that there is no metastatic disease. As is the case with primary cystectomy, an exploratory laparotomy is performed first to ensure that there is no involvement of the lymph nodes, omentum, or other organ sites. Even in patients who have no extravesical spread, the morbidity of radical cystectomy can be significant although the operative mortality is low (1% to 3%). Although salvage cystectomy is the preferred approach, it may not be possible for a patient who has received a full course (greater than 65 Gy) of external-beam RT and has bulky residual disease. For these patients, salvage chemotherapy is advised, generally with a regimen that is non-cross-resistant to the one that the patient has previously received. Those treated with single-agent cisplatin can be considered a standard three- or four-drug regimen, whereas those who have already received a three-drug (eg, MCV)

or four-drug (eg, M-VAC) regimen may be considered for therapy with paclitaxel, gemcitabine, or ifosfamide, as outlined below under salvage chemotherapy. If the patient has not received RT, a course of RT should be considered. Metastatic disease is managed with salvage chemotherapy using a regimen to which the patient has not been previously exposed.

### **Non-organ-confined disease (T3a, T3b/T4a, T4b)**

The primary surgical treatment for a tumor that has extended beyond the confines of the bladder wall and that is still considered resectable, based on the mobility of the bladder, is radical cystectomy with consideration of neoadjuvant chemotherapy, as outlined previously. Except in highly selected cases (see below), bladder preservation is not an option in such patients since the proportion rendered tumor-free using chemotherapy alone is generally less than 10%. Tumors that are pathologic stage T3 or T4 with nodal involvement or vascular invasion have a high risk (greater than 50%) of systemic relapse and, therefore, may be considered for treatment with adjuvant chemotherapy or radiotherapy. The followup schema is the same as that previously outlined for high-risk patients in the section on adjuvant chemotherapy. Owing to the high risk of systemic relapse in this group, based on historical series using surgery alone, a number of groups are also investigating combined-modality approaches using neoadjuvant chemotherapy followed by surgery or neoadjuvant chemotherapy and radiation followed by surgery. If possible, these patients should be placed on clinical trials. Bladder preservation can be considered in selected cases in which there is no

palpable mass on EUA and no hydronephrosis. This approach should also be used in the context of an investigational protocol, or be considered for patients who are deemed unsuitable for surgery based on medical comorbidities. Evaluation with cystoscopy, biopsy, or cytology study is necessary following the bladder preservation treatment. If resectable tumor is found, surgical approach with cystectomy is considered. Patients with unresectable tumors undergo salvage therapy. If no tumor is detected, observation, consolidation with chemotherapy and concurrent RT, or adjuvant chemotherapy is recommended. The general approach to this bladder-sparing strategy for these patients is similar to that outlined previously under bladder-sparing strategies in patients with organ-confined disease. Patients are treated with a course of induction therapy (eg, RT with concurrent chemotherapy, neoadjuvant chemotherapy alone or neoadjuvant chemotherapy plus RT with or without concurrent chemotherapy) with a deferred decision on management of the primary lesion.

### **T4a, T4b disease**

Patients with unresectable disease, defined as a fixed bladder mass, or those with positive nodes prior to laparotomy are considered for chemotherapy alone or chemotherapy with RT. An initial stratification is based on the results of transaxial imaging. For patients who show no nodal disease on CT scans, the treatment recommendation includes two to three courses of chemotherapy with or without RT followed by cystoscopy and CT scan. If the tumor has responded, options include surgery or consolidation chemotherapy with or without RT. If no

response is noted, chemotherapy with RT or a new chemotherapy regimen can be used. In highly selected T4a node-negative patients, surgery with or without chemotherapy could be another treatment option. If pelvic lymph nodes greater than 2 cm on imaging are documented, a biopsy is advised to exclude nodal spread. Baseline renal function, the presence or absence of cardiac disease, and overall performance status must also be considered when making a treatment recommendation. Patients with a good performance status and no significant comorbid disease may be considered for chemotherapy with or without RT if their nodes are positive. If complete response is obtained, patients may be managed with observation, boost with RT, or surgery may be contemplated. Chemotherapy options are discussed below under metastatic disease, whereas combined-modality approaches using chemotherapy and RT are discussed above. For patients who cannot tolerate multidrug combinations with radiotherapy, an alternative is to use RT with a radiation sensitizer, such as cisplatin, administered starting on day 1 and day 21, or 5-FU with a variety of schedules. Patients are initially treated with 45 Gy of radiation to the pelvis and bladder, with a boost of approximately 20 Gy to sites of disease within the bladder. In highly selected patients with metastatic disease who have a complete systemic response to chemotherapy, salvage surgery may be performed to render the patient disease-free. Data from several groups show that this aggressive approach can result in long-term survival. Prior to exploratory surgery, metastatic disease must be excluded with appropriate imaging studies. If the exploration is negative for metastases within the abdomen, salvage surgery can

be performed. Patients who have residual invasive disease in the bladder or nodal spread after combined-modality therapy have a high risk of local and systemic relapse and should be followed as outlined previously. If there is no response, a change in chemotherapy is recommended or, depending on the patient's symptoms from the primary lesion, palliative radiotherapy may be considered.

### Metastatic disease

Patients who present with unresectable or metastatic disease or who subsequently develop metastatic disease are generally treated with systemic chemotherapy or radiotherapy. These patients should undergo a staging evaluation that includes a chest x-ray, transaxial imaging of the abdomen and pelvis, and determination of creatinine clearance. The specific chemotherapy regimen recommended depends, in part, on the presence or absence of medical comorbidities, such as cardiac disease and renal dysfunction, along with the risk classification of the patient based on disease extent. In general, long-term survival with combination chemotherapy alone has been reported only in good-risk patients, defined as those with good performance status, no visceral (liver, lung) or bone disease, and normal alkaline phosphatase or lactic dehydrogenase (LDH) levels. Poor-risk patients, defined as those with a poor performance status or visceral disease, have consistently demonstrated very poor tolerance to multiagent combination programs and few complete remissions—a prerequisite for cure. Currently there are three active drug types that are active in the management of advanced bladder cancer: cisplatin, the taxanes, and gemcitabine. Varieties of two

or three drug combinations of these agents have demonstrated clinical benefit. A commonly used combination in good-risk patients is a multidrug cisplatin-based regimen, such as M-VAC or MCV. An alternative is cisplatin and gemcitabine, based on a direct comparison to M-VAC. More recently, the taxanes have been shown to be active as both front-line and salvage therapies, and both gemcitabine and ifosfamide have shown utility as salvage therapy. Based on these results, a number of groups are exploring two- and three-drug combinations using these agents, with and without cisplatin, as initial therapy. A major determinant of the regimen to be used is the performance status of the patient, and the use of regimens with lower toxicity profiles is recommended in patients with compromised liver or renal status or serious co-morbid conditions. The regimens effective for urothelial carcinoma (transitional cell) histologies have limited efficacy for patients with non-urothelial (non-transitional cell) carcinomas. These individuals are often treated on the basis of the identified histology (eg, adenocarcinomas with regimens typically used for colon cancers, and squamous tumors with regimens typically used for tumors originating in the head and neck). However, overall experience with chemotherapy in non-urothelial carcinomas (non-transitional cell tumors) is limited. Independent of the specific regimen used, patients with metastatic disease are reevaluated after two to three cycles of chemotherapy, and treatment is continued for two more cycles in patients whose disease responds or remains stable. Surgery or radiotherapy may be considered in patients who show a major partial response in an unresectable primary

tumor or who have a solitary site of residual disease that is resectable after chemotherapy. In selected series, this approach has been shown to afford a survival benefit. If disease is completely resected, consideration can be given to two additional cycles of chemotherapy depending on patient tolerance. Those in whom surgery or radiotherapy are not considered options are generally treated with chemotherapy for a maximum of six cycles depending on their response.

If there is no response after two cycles or if significant morbidities are encountered, a change in therapy is advised. The change should take into account the patient's current performance status, extent of disease, and the specific prior therapy that has been administered. The same would apply for patients who have relapsed systemically after adjuvant chemotherapy. Patients who cannot tolerate cisplatin-based therapy because of medical comorbidities may be considered for a carboplatin-based regimen or, alternatively, paclitaxel or gemcitabine as a single agent. For salvage therapy, paclitaxel (if it has not been used earlier), gemcitabine, or ifosfamide is advised depending upon the patient's current status

# Prostate Specific Antigen (PSA)

## Commentary

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With the advent of PSA screening, a greater number of men require education about prostate cancer and how it is diagnosed, staged, and treated in order to select the most appropriate treatment. However, one should keep in mind that it is a prostate specific and not a prostate cancer specific antigen. So prostate specific antigen (PSA) and digital rectal examination (DRE) should be offered together. Information should be provided to patients regarding potential risks and benefits of intervention. Most prostate cancer is slow growing - only 30 percent of men diagnosed with prostate cancer will die from the disease.

### Historical background

It was first identified in seminal plasma in 1971 by Hara and associates. Wang and associates<sup>1</sup> isolated it from prostate tissue. Since the test was introduced into clinical practice in 1986, the early diagnosis and management of prostate cancer has been revolutionized and much has been learned about the strengths and weaknesses of this assay.

### Structure

PSA is a 33-kd protein consisting of a single-chain glycoprotein of 237 amino acid residues, 4 carbohydrate side chains, and multiple disulfide bonds. PSA is homologous with the proteases of the kallikrein family and is a androgen-

regulated serine protease. PSA is synthesized in the ductal and acinar epithelium as an inactive 244 amino acid proenzyme (pro-PSA) that is activated by cleavage of seven *n*-terminal amino acids. PSA that enters the circulation intact is rapidly bound by protease inhibitors, primarily alpha1-antichymotrypsin and  $\alpha_2$  macroglobulin, although a fraction is inactivated in the lumen by proteolysis and circulates as free PSA. This proteolytic inactivation, as well as the cleavage of pro-PSA to PSA, is less efficient in prostate cancer.

The upper limit of normal PSA is 0-4 ng/ml. PSA is abundant in seminal fluid, at concentrations up to 3.0 mg/ml, a million times more abundant than in serum. Thus, there is considerable overlap in values between patients with prostate cancer and those with benign

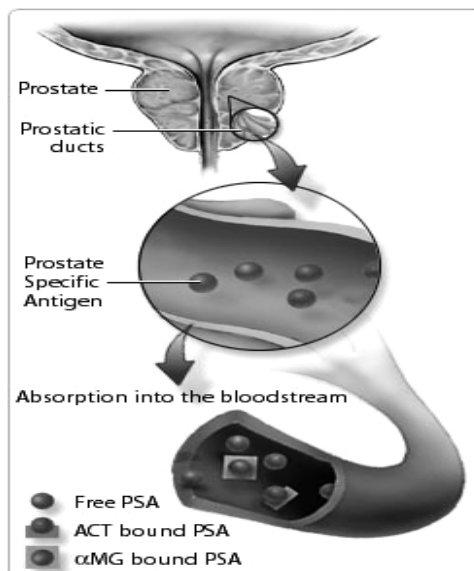
conditions, such as benign prostatic hyperplasia and prostatitis. Half-life of PSA is 2.2-3.2 days.

### Function

The enzymatic activity of PSA induces liquefaction of seminal clot. Seminal clotting is because of seminogelin 1 and 2 and fibronectin. PSA targets seminogelin component and liquefy seminal clot and the release of spermatozoa, hence helps in sperm motility.

### Clinical application

The sensitivity for detecting cancer with a PSA greater than 4ng/ml is approximately 80%. For men with a PSA level of 4 to 10 ng/ml, ultrasound-guided biopsies detect cancer in 25%, of which 75% are pathologically confined. If the PSA is greater than 10 ng/ml, 60% have cancer, but only 40% to 50% are confined. The specificity is 15% to 20% that is, one of five or six men without cancer will have an elevated PSA. Poorly differentiated adenocarcinoma produces less PSA for same volume as compared to well-differentiated cancer. Although PSA levels cannot be used to diagnose prostate cancer and is not a specific prostate cancer marker, the benefits of PSA testing outweigh its drawbacks. Serum total PSA level are increased in prostate cancer, and PSA screening has dramatically altered prostate cancer presentation and management. Under pathologic



conditions, PSA reaches serum through the disrupted epithelial basement membrane, passing into capillaries and lymphatics. Unfortunately, although high PSA levels are predictive of advanced prostate cancer, a large fraction of organ-confined cancers present with much lower total PSA values that overlap those levels found in men without prostate cancer. Measurement of free versus total PSA can increase specificity for prostate cancer, and tests under development to measure forms of pro-PSA may further enhance the ability to detect early-stage cancer.

### Problems in PSA testing

- The lack of standardization between assays and laboratories is a major problem. Efforts are underway to correct this situation, but inconsistency between assays may make comparisons difficult.
- Another problem involves the handling and processing of the blood samples in physicians' offices or in the laboratories. The blood sample should be centrifuged and the serum should be separated within 2-3 hours. If the assay is not performed within the next 2-3 hours, the serum should be frozen. Once frozen at -20°C or -70°C, the enzyme remains stable for at least a month.
- The next problem involves the decision to perform a biopsy in patients with PSA levels in the range of 4-10 ng/ml. In clinical practice, the test often is repeated after a 2- to 4-week course of antibiotics such as doxycycline or a fluoroquinolone, and, if confirmed, a biopsy is performed. The intention is to use the antibiotics to treat any prostatitis present. Prostate cancer would,

course, not be affected by standard antibiotics. The fPSA, PSA<sub>d</sub>, and other manipulations do not replace clinical judgment.

### Change in PSA levels

- PSA value change occurs after biopsy, TURP and prostatitis, so one should wait for 3 to 6 weeks before performing PSA again<sup>2</sup>.
- The serum PSA level can be altered by various medications like Finasteride and dutasteride, 5-alpha reductase inhibitors that are commonly prescribed for the treatment of BPH, can produce a decrease in total prostate levels by 50% within 6 months of therapy. This alteration fluctuates widely, ranging from -81% to +20%. After 3-4 months of therapy, another PSA measurement can be obtained to establish a new baseline. Alpha1-aDR energetic antagonists, which are frequently used to treat the symptoms of BPH, do not alter PSA levels.
- Herbal products such as saw palmetto do not affect PSA levels.
- Any medications that alter testosterone levels can affect the serum PSA. The use of luteinizing hormone-releasing hormone (lhrh) agonists and antagonists to stop production of testosterone by the testicles is a cornerstone in the treatment of prostate cancer. This manipulation produces a profound reduction in PSA levels, usually making them undetectable. Raising testosterone levels may increase PSA levels, but not to the same degree as reducing testosterone production.

Some helpful hints for obtaining a

maximally accurate PSA test include:

- Abstain from ejaculation for 2 days prior to having a PSA test
- Take history of any drugs used to treat BPH and baldness, will likely lower PSA levels.
- Be sure that the biopsy is performed *after* drawing blood for the PSA test, as the it can artificially raise PSA levels.
- Herbal supplements can also affect PSA levels. Be sure to ask about any supplements that patient is taking before the PSA test.

To increase the sensitivity and specificity various other forms of PSA can be calculated e.g. age specific PSA, PSA velocity, PSA density, free and total PSA, PSA transition zone and PSA doubling time.

### Age-specific reference ranges

The standard PSA reference range of 0.0-4.0 ng/ml does not account for age-related volume changes in the prostate that are related to the development of BPH. Oesterling et al (1993) presented the concept that age-related reference ranges would improve cancer detection rates in younger men and would increase the specificity of PSA testing in older men. Using reference ranges of 0-2.5 for men aged 40-49 years, 0-3.5 for men aged 50-59 years, 0-4.5 for men aged 60-69 years, and 0-6.5 for men aged 70-79 years, they reported an overall specificity of 95%. A different reference range was used for black men<sup>3</sup>. With a PSA range of 0-2 for men aged 40-49 years, specificity was 93%. A PSA range of 0-4 produced a specificity of 88% for men aged 50-59 years, a PSA range of 0-4.5 produced a specificity of 81% for men aged 60-69

years, and a PSA range of 0-5.5 produced a specificity of 78% for men aged 70-79 years.

The use of age-specific reference ranges in clinical practice results in the diagnosis of more cancers in men younger than 60 years at the expense of more negative findings on biopsy. However, early potentially curable cancers should be diagnosed in this age group. An increasing number of men in the fifth and sixth decades of life are being diagnosed with significant cancers as a result of using age-specific reference ranges in addition to PSA density and PSA velocity. No easy answer is available to decide when biopsies may be avoidable and when they are necessary. Clinical judgment and experience dictate the answer to this dilemma until a perfect test is developed, and that is unlikely. The influence of race on age-specific reference ranges has been studied. Reports indicate that PSA levels are higher in black men compared to white men, even when controlled for age, clinical stage, and Gleason grade.

### Percent free PSA

This test measures how much PSA circulates freely in the blood and how much is bound with other proteins. Free PSA is reported as a percent. The more free PSA that is present the better it is (or the more likely a man is to be "free" of cancer). So, if a man has an elevated total PSA, but most of it is "free PSA," then it is most likely coming from BPH rather than cancer<sup>4</sup>. Conversely if most of the total PSA is coming from PSA that is bound to proteins, it is more likely that the patient will have cancer. In one study, researchers used a free-PSA cutoff range

of 19% in men with total PSA levels between 3 and 4 and detected 90% of all cancers. In another study of men with total PSA levels between 4 and 10, biopsies were performed only in men with free PSA of less than 25% of the total PSA. They detected 95% of the cancers and reduced unnecessary biopsies by 20%. The lower the ratio of free-to-total PSA, the higher the likelihood of cancer. Using 25% as the cutoff, 95% of cancers can be detected in both African Americans and whites. A cutoff of 22% maximizes cancer detection and minimizes unnecessary biopsies. Generally, these percents are useful in patients who have a PSA level in the range of 4-10 ng/ml.

### PSA density

In 1992, Benson et al<sup>5</sup> introduced the concept of PSA<sub>d</sub> to correlate PSA and prostate volume. PSA density is the value

prostate cancer and BPH in men whose PSA levels are 4-10 ng/ml<sup>6</sup>. The value of PSA<sub>d</sub> is limited because of its dependency on the individual performing the prostate volume measurement. In addition, the BPH volume does not always correlate with serum PSA values because of the variation that exists between individuals in their epithelial-to-stromal ratios. PSA is made only by the epithelial cells, which produces a lower PSA level even though the total volume of the prostate is high. The value of PSA<sub>d</sub> could improve the detection rate of cancer at a cutoff of 0.15.

### PSA velocity

In 1992, Carter<sup>7</sup> et al introduced the concept of PSA-v in an effort to improve the ability of PSA to detect prostate cancer. Calculating the PSA velocity tracks changes in the PSA blood level over time - for example, how quickly the PSA level rises over the course of several months. PSA velocity may aid the interpretation of borderline PSA results by measuring whether the PSA levels are increasing over a short period of time. The test is used as a tool to keep track of how PSA levels change, but it is not used to diagnose prostate cancer. If PSA increases dramatically in a short period, it may be one indicator that prostate cancer has progressed. PSA-v is used to monitor the change in PSA over time using longitudinal measurements. Greater changes in PSA-v were detected in men with cancer compared to those without cancer 5 years before the diagnosis was made. Additional studies have shown that this difference can be detected up to 9 years before prostate

Probability of Prostate Cancer			
Standard PSA	Probability of cancer	Percent free PSA	Probability of cancer
0-2 ng/mL	1%	0-10%	56%
2-4 ng/mL	15%	10-15%	28%
4-10 ng/mL	25%	15-20%	20%
> 10 ng/mL	> 50%	20-25%	16%

of the PSA divided by the size of the prostate, which can be determined by a transrectal ultrasound (TRUS). The likelihood of prostate cancer is increased when the PSA<sub>d</sub> value is high. In other words, if you have a relatively small prostate that is producing large amounts of PSA, there is a greater likelihood that cancer is present. If the prostate is large relative to the PSA score, there is a greater chance that BPH to blame. Theoretically, PSA<sub>d</sub> could help distinguish between

cancer diagnosis.

PSA-v is calculated using the following equation:

$$I/2 \left( \frac{PSA2 - PSA1}{\text{time 1 in years}} + \frac{PSA3 - PSA2}{\text{time 2 in years}} \right)$$

PSA1 = first PSA measurement  
PSA2 = second PSA measurement  
PSA3 = third PSA measurement

At least 3 PSA measurements are needed during a 2-year period or at least 12-18 months apart to obtain maximal benefit from the results.

A PSA-v of 0.75 ng/ml or greater per year was suggestive of cancer (72% sensitivity, 95% specificity). A PSA-v of 0.75 ng/ml or greater correlated with the diagnosis of cancer in 72% of the patients, and only 5% had no cancer. The limitations of PSA-v testing include that it is difficult to calculate, that PSA is not cancer specific, and that PSA varies significantly with time and with different assays. Nevertheless, a PSA-v greater than 0.75 ng/ml per year is useful in some situations in helping to decide the need for initial or repeat biopsy.

### PSA transition zone density

Kalish introduced prostate-specific antigen density of the transition zone (PSA-tz) as a refinement of the original PSA-d. This refinement is predicated on 2 assumptions, first measuring transitional Zone volume by transrectal ultrasonography is more accurate than measuring the entire prostate volume because of the difficulty in measuring the true border of the apex in the longitudinal view, and secondly most of the PSA entering the circulation arises from the tz.

### Peripheral zone fraction

Zisman et al (2000) have offered a new

index using the peripheral Zone fraction of PSA to predict the presence of prostate cancer in men with PSA levels of 4-10 ng/ml. They point out that the pz contributes little to the amount of tPSA. The peripheral Zone fraction can be calculated using the following formula:

$$\frac{TPSA \times (\text{total prostate volume} - \text{tz volume})}{\text{total prostate volume}}$$

Pz volume is measured by subtracting the tz volume from the entire prostate volume while neglecting the central zone. They compared the positive and negative predictive values using tPSA, PSA-d, PSA-tz, and prostate-specific antigen peripheral zone density (PSA-pz). The efficacy of PSA and PSA-tz was similar, at 60%. PSA-pz was 70% and PSA-d was 80%. The negative predictive values were superior to the positive predictive values. The negative predictive value for PSA and PSA-d ranged from 78-83% and 78-88%, respectively. The negative predictive value of PSA-tz and PSA-pz ranged from 87-92% and 81-100%, respectively. Using roc curves, both PSA-tz and PSA-pz were significantly larger than PSA and PSA-d. When patients with negative DRE findings were studied using the roc curve, the area under the PSA-pz curve was larger than that of the PSA-tz curve.

### PSA doubling time

Patel<sup>8</sup> et al in 1997 reported that PSA doubling time was a better predictor of time to clinical recurrence than preoperative PSA, stage, and pathological gleason score. A PSA doubling time of 6 months or less after surgery indicated metastatic disease. They reported that 80% of 77 patients with detectable PSA postoperatively and a doubling time longer than 6 months remained clinically disease-free,

compared to 64% with a PSA doubling time shorter than 6 months. Pound and associates (1999) used a doubling time of 10 months to derive similar conclusions. They cautioned against treating patients with long PSA doubling times too early because most of these men lived for many years before evidence of clinical disease was detected.

### PSA after treatment

PSA-v and pathology stage have been studied to determine treatment failure and the need for additional intervention. A detectable PSA level in a patient with micrometastatic lymph node disease, a gleason score greater than 7, and/or seminal vesicle invasion indicates distant metastatic disease. Partin et al<sup>9</sup> in 1994 used multivariate analysis to study PSA-v, gleason score, and pathologic stage to predict local recurrence and distant metastases. In patients whose PSA became detectable a year or more following surgery, a PSA-v less than 0.75 correlated with local recurrence in 94% of patients, while a velocity greater than 0.75 predicted distant disease in more than 50% of patients. A detectable PSA within the first 2 postoperative years is indicative of distant metastases and correlates with other risk factors such as stage and grade. This is important in determining which patients might benefit from local radiation therapy following prostatectomy. A pattern of PSA rise after local therapy distinguishes between local and distant recurrence. Distant disease can be predicted if the PSA does not become undetectable following radical prostatectomy, begins to rise within 12 months, or has a doubling time of 6 months. The same characteristics apply to radiation therapy and cryotherapy, although the time to nadir is prolonged. Patients whose PSA level

becomes detectable 24 months or more after radical prostatectomy likely have local recurrence. Patients with PSA doubling times of 12 months or more following surgery, radiation therapy, or cryotherapy are likely to have local recurrence.

### Significance of PSA testing

- DRE and TRUS are examiner dependant but PSA is an objective test with highest positive predictive value for cancer prostate.
- It increases the lead time for cancer prostate thus result in detection of cap that are more often confined to prostate as compared to cancer discovered by DRE alone.
- It can be used to diagnosis as well as to monitor the response of treatment in cancer prostate.

### Recommendation for PSA screening

Cost-effective guidelines for PSA testing that define age to start, age to stop, testing interval, and PSA threshold for screening have not been clearly defined. Although PSA testing detects more cancers than DRE, a combination of the 2 methods is better. Screening should be done

- Asymptomatic men should begin at age 50 years after a discussion of the potential risks and benefits of screening and should be targeted at those men with more than a 10-year life expectancy.
- Annual PSA screening in men at higher risk, such as African Americans or Scandinavian race and those with an affected first-degree relative, should be tested earlier, at age 40 or 45 years.

### Prostate specific antigen and

### breast cancer

PSA in breast cancer is associated with the expression of estrogen receptor and progesterone receptor. A number of studies have indicated that elevated PSA levels are a favourable prognostic factor in breast cancer. In particular, a large cohort study of 953 women with breast cancer (Yu, 1998)<sup>10</sup> found that survival and relapse free survival were significantly better in patients with levels higher than the 30th percentile of PSA compared to PSA-negative patients. PSA expression was significantly associated with smaller tumours, smaller proportion of S-phase cells, diploid tumors and younger age. PSA remained a significant independent prognostic factor after taking into account other clinical and pathological features.

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# Complications following Abdomino perineal Resection for Carcinoma Anorectum

Original  
Article

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## Abstract

The objective of the study was to analyze study the operative morbidity and mortality and disease recurrence after abdominoperineal resection (APR) for carcinoma anorectum in 100 patients operated at our institution. 100 patients operated for APR at our institution between September 1992 and July 2004 were included in our study. These patients were followed upto November 2004. Patients not surgically treated at our center but outside were excluded from the present study. 54 males and 46 females, who underwent APR at our center were studied. The mean age was 53.07 years. The most common presenting complaint was bleeding per rectum. Three patients developed intra-operative complication and there were, two immediate post operative mortalities in our 100 patients. The immediate post operative complications observed were abdominal and perineal wound infection and dehiscence. The delayed post operative complications were genito-urinary complications seen in 32 patients, adhesive small bowel obstruction in 23 patients, colostomy related complications in 4 patients and incisional hernia in 6 patients. In terms of disease recurrence, after APR in the follow up period, 11 patients developed distant metastasis, most common being Liver metastasis followed by inguinal Lymph Node metastasis in 6 patients. Local disease recurrence in pelvis was seen in 23 patients. Abdominoperineal

resectin (APR) remains the “gold standard” for low lying advanced carcinoma anorectum. APR carries low mortality but high morbidity rate with respect to both immediate and delayed post operative complications.

**Key words-** Abdominoperineal Resection, Carcinoma Anorectum, Complications, Distant metastasis, local recurrence.

## Introduction

Colorectal cancer is the most common cancer of gastro intestinal tract. In women, Gastro intestinal cancer is 2<sup>nd</sup> only to cancer breast as a cause of cancer related death. In men it is the third most lethal cancer preceded by lung and prostate. Approximately one half of these tumors are located in the rectosigmoid region. It was estimated that approximately 13000 new cases of colorectal cancer occurred in the USA in 2000 and approximately 500 patients would die because of this disease. Recent data indicate that in the USA, the average age related incidence of colorectal cancers for males is 46.5 and for females is 37.2 per lac per year. Rectal cancer is similar to colon cancer in that the majority of malignant neoplasms of rectum are Adenocarcinoma. The management of Squamous Cell Carcinoma differs significantly from Adenocarcinoma. Adjuvant treatment that is radiotherapy and chemotherapy have a definite role in both locally advanced carcinoma anorectum and for Duke's C Stage. Nigro's Chemoradiation

regimen has become the first choice for the carcinoma anal canal ahead of Abdomino-perineal resection. With improvement in diagnostic techniques and with advances in adjuvant therapy, there is a definite trend toward sphincter preserving techniques instead of APR, whenever possible. Complications resulting from surgical management of rectal cancers besides those associated with any major abdominal surgeries like Sepsis, Myocardial infarction, Pulmonary embolism, and wound infection, include - Injury to sexual function - A 50% incidence of significant impotence in men following resection of rectum for cancer has been reported. Malfunctioning of urinary system - since perineal dissection of rectum comes very close to membranous urethra. Patients can have urinary incontinence due to loss of neurological control of urethra. Stoma related complication - Ischemia, Retraction, hernia, Stenosis, Prolapse and Fistula.

Perhaps the most important prognostic consideration lies in the status of cancer with respect to distant metastasis and local recurrence. Cancer rectum spreads locally via the lymphatics and direct invasion, which is mainly in the upward direction along the superior hemorrhoidal vessels.

Hematogenous spread to the liver through the portal system occurs in 30% to 50% of patients dying of rectal cancer. Other sites of distant hematological metastasis include lung, bone, brain,

spleen and ovaries. Local recurrence in the pelvis after surgical resection is common and can occur with and without metastatic disease. Death in patients with pelvic resection is characterised by extreme discomfort and poor quality of life. This situation has stimulated efforts to eliminate pelvic recurrence and has lead to use of adjuvant Pre op radiotherapy. This study has been done with the objective to highlight that operative mortality and morbidity and disease recurrence after APR in 100 Patients operated at our institution between September 1992 and July 2004.

Abdomino perineal resection (APR) has remained the standard treatment for malignancies of distal one thirds rectum since it was first described in 1908 by Ernest Miles. APR shares with mastectomy the honour of dominating surgical thoughts about a major malignancy for the last about hundred years of surgical practice<sup>2</sup>. APR is indicated in -poorly differentiated (G-3) or T3 lesions, lower thirds of rectum; cancers located less than 3 cm proximal to dentate line or 5 cm from anal verge are generally not amenable to restorative resection; advanced rectal cancer (T4) as palliative resection, especially in elderly/poor risk patients; as salvage procedure for local recurrence or if there is biopsy proven tumor after initial chemo radiation, as suggested by Norman Nigro, for anal canal cancers<sup>3</sup>.

### Material and Methods

A combined retrospective as well as prospective analysis of the clinical and pathological data along with results after surgery in terms of complications & disease recurrence was done in our study. Analysis of 75 patients of carcinoma anorectum undergoing abdomino perineal resection (APR) at our center

between September 1992 to December 2001 was done retrospectively and 25 patients operated between January 2002 to July 2004 and followed up to November 2004 were analyzed prospectively. The case records of the patients were obtained from the medical records department and scrutinized. The inclusion criteria for patients in our study were-Histo-pathologically proven cases of carcinoma anorectum; Patients operated at our center only. Those patients who were operated outside our center were not included in the present study.

### Results

In our study group of 100 patients (75 studied retrospectively and 25 studied prospectively) operated for abdominoperineal resection, there were 54 males and 46 females. Male to female ratio was 1.17:1. Mean age was 53.07 years and median age was 53 years. The youngest patient in our study was 28 years old and the oldest patient was 89 years old. The most common presenting complaint of the patients studied was bleeding per rectum seen in 80 patients (80%) followed by altered bowel habits i.e. constipation or diarrhea in 51 patients (51%). Bowel obstruction was seen in 1 (1%) patients.

**Table - 1, Clinical profile of retrospective & prospective group of patients**

	Retrospective (N=75)
Sex (Male/Female)	(38/37)
Mean Age (year)	52.45 ± 11.99
<b>Chief Complaints</b>	
Bleeding per rectum	60
Altered Bowel Habits	38
<b>Distance of Growth from anal verge</b>	
0-2 cm	20
2-4 cm	37
> 4 cm	18
<b>Histopathology</b>	
Adenocarcinoma Anorectum	62
Squamous cell carcinoma	8
Malignant Melanoma	3
<b>Staging (Post Operative)</b>	
Dukes' B	43
Dukes' C	24

**Table -2, Showing incidence of various post-operative complications after APR**

	Retrospective (N = 75)
Intra operative complications	3
Operative mortality	2
<b>Abdominal wound complications</b>	
Wound infection	9
Wound Dehiscence	11
<b>Perineal Wound complication</b>	
Wound infection	9
Wound Dehiscence	2
Genito urinary Complications	24
Adhesive bowel obstruction	20
Colostomy related complications	2
Incisional Hernia	4

**Table - 3, Showing Disease recurrence after APR**

Distant Metastasis	Retrospective (N = 75)	Prospective (N = 25)
Total	7	4
Liver	6	3
Lung	3	-
Brin	2	-
Dukes' B	4	1
Dukes' C	1	-
Malignant Melanoma	2	-
<b>Inguinal Lymph Node Metastasis</b>		4 2
Dukes' B	3	1
Dukes' C	1	-
Malignant Melanoma	1	-
<b>Local Recurrence</b>		
Total	17	6
Prostate	2	-
Posterior Vaginal wall/ Vault recurrence	5	-
Dukes' B	14	1
Dukes' C	3	3
Ana plastic Malignancy	-	2

The distance of the growth from the anal verge was (0-2) cm in 34 patients (34%), (2-4) cm in 43 patients (43%) and (> 4)cm in 23 patients (23%) operated for APR. The distance of growth from anal verge remains the critical criterion for deciding about sphincter preservation or not in surgery for carcinoma anorectum.

Post operatively, adenocarcinoma anorectum was the most common histopathology, seen in 81 patients (81%) followed by squamous cell carcinoma in 11 patients (11%). Malignant melanoma was seen in 3 patients (3%). Dukes' B (T3/ T4 N0 M0) was the most common histopathological stage seen in 57 (57%) patients followed by Dukes' C (Any T N1 M0) in 32 patients (32%). In our study group, three patients had intraoperative complications: two patients had ureteric injuries during dissection. For which primary repair was intestinal obstruction with successful in one but the other patient required boari flap construction and psoas hitch operation. One patient developed anterior sacral venous plexus ooze, which was managed successfully with packing. There were two immediate post operative mortalities (2%) in our 100 patients, seen with in 30 days of surgery. The cause of death in one patient was intestinal obstruction with septicemia and acute renal failure. The second mortality was in a known case of bronchial asthma, who died because of respiratory failure and septicemia. The other post operative complications observed in our study were abdominal wound infection in 10 patients (10%),

abdominal wound dehiscence in 12 patients (12%), out of these 11 patients required mass closure. Perineal wound infection was seen in 13 patients (13%) and perineal wound dehiscence was seen in 3 patients (3%).

The delayed complications after APR observed in our study were: Genitourinary complications seen in 32 patients (32%) with incontinence of urine being the most common, seen in 12 patients followed by symptomatic urinary tract infection, retention of urine and radiation cystitis, all seen in four patients each. Difficulty in passing urine, post operatively was seen in three patients. These patients with retention of urine and difficulty in passing urine required either urethral dilatation (in three patients) or cystoscopy and channel's operation (in two patients). The rest were managed by urethral cauterization. Adhesive small bowel obstruction was seen in 23 patients (23%). Among these 23 patients, 16 had received local radiotherapy prior to episodes of obstruction. Four patients had episodes of repeated small bowel obstruction. Exploratory laparotomy with adhesiolysis was done in 8 of these 23 patients. Resection - anastomosis of the small bowel was done in 3 patients. Right hemi-colectomy and ileotransverse anastomosis was required in 5 patients. Conservative management was successful in 6 patients and one patient died because of septicemia and acute renal failure. Colostomy-related complications were seen in 4 patients (4%). There were two cases each of colostomy stenosis and of paracolostomy hernia, all four of which required surgical repair.

Incisional hernia as a delayed post operative complication was seen in 6 of our 100 patients (6%).

Only one of these patients underwent hernioplasty with polypropylene mesh. In terms of disease recurrence after APR in the follow up period, 11 of our patients (11%) developed distant metastasis. Among these liver metastasis were the most common, seen in 9 patients (9%) followed by Lung metastasis in 3 patients (3%) and Brain metastasis in 2 patients (2%). In these 23 patients, Dukes' B stage was seen in 15 patients, Dukes' C in 6 patients and two patients had anaplastic (Undifferentiated) type of malignancy. Five of our female patients (5%) developed posterior vaginal wall or vault recurrence whereas two of our male patients (2%) developed local recurrence involving the prostate. The mean period of detection of local recurrence after APR was 11.1 months and two deaths were reported in these 23 patients where as the rest were lost of follow up.

## Discussion

Abdominoperineal resection (APR) has been regarded as the "gold standard" for the treatment of rectal cancers for many years.<sup>3</sup> Several authors have described the complications & disease recurrence after APR over the years. In our study of 100 patients operated for APR, there were 54 males (54%) and 46 females (46%) with mean age of 53.07 years and age range of 28-89 years. Petrelli, Nagel et al<sup>4</sup> found 38 males (68%) and 18 females (32%) among their 56 patients operated for APR. They found the mean age of their patients to be 59 years with age range of 37-80 years. Zaheer, Pemberton et al<sup>1</sup> observed bleeding per rectum as the most common presenting complaint: in 61% of their 514 patients operated for APR followed by change in bowel habits seen in 33% patients. Intestinal obstruction was seen in 1% patients. Almost the same

pattern was seen in our study with 80% patients presenting with bleeding per rectum, 51% with altered bowel habits and 1% with bowel obstruction. Fleshman, Wexner et al<sup>5</sup> quoted an incidence of adenocarcinoma anorectum of 92% (140 patients) and of squamous cell carcinoma of 6.6% (10 patients) in their study group of 152 patients. In our study the incidence was 81% (81 patients) and 11% (11 patients) respectively. Petrelli, Nagel et al. found an incidence of Dukes' B of 48.2% and of Dukes' C of 34% in their 56 patients. In our study, the incidence was 57% and 32% respectively. With regards to intra-operative complications, Petrelli, Nagel et al have quoted haemorrhage from sacral venous plexus in 2 patients (3%) and transected left ureter in one patient (2%) amongst their 56 patients. The same authors have described 2 deaths in their 56 patients (3%) within 30 days of surgery. The cause of death in one was exsanguinating haemorrhage from sacral venous plexus and due to pulmonary embolism in the other. Zaheer, Pemberton et al observed an overall mortality of 1.8% after APR. Rosen, Veidenheiner, Coller<sup>9</sup> have reported an overall mortality of 1.7% in 230 patients who underwent APR. In our study the incidence of intraoperative complications was 3% and the post operative mortality was 2%.

Amongst the wound complications after APR, Luna Perez et al<sup>6</sup> found an incidence of 14.6% (20/137) of perineal wound complications. On the other hand, Slanetz, Herter et al<sup>7</sup> found abdominal wound complications in 5.8% (11/190) patients. In our study, the incidence of perineal wound complications was 16% and of abdominal wound complications was 22%. The greater incidence of abdominal wound complications in our

study was likely due to poor general condition, debility and associated comorbid illnesses in our patients. With regards to genitourinary complications, Slanetz, Herter et al. quoted an incidence of 35% (66/190) patients, while Petrelli, Nagel have stated an incidence of 34% (19/56) with urinary retention being the most common urinary complaint followed by incontinence of urine. In our study, 32% of our 100 patients developed genitor-urinary complications with space bar incontinence of urine being the most common complaint followed by retention of urine.

Nissan, Guillem et al<sup>8</sup> reported 9.9% (29/292) incidence of adhesive small bowel obstruction amongst their patients 20% of these patients (6/29) had received local radiotherapy. Our incidence of adhesive bowel obstruction was greater: 23% but 69.5% of these patients (16/23) had received local radiotherapy. Hence local radiotherapy, especially post operative radiotherapy can contribute to increased incidence of adhesive bowel obstruction. With regards to colostomy related complications, Petrelli, Nagel et al found that only one of their 56 patients required revision of colostomy for these complications. Our incidence of colostomy-related complications was 4%. Hence contrary to general belief, APR is associated with low incidence of colostomy-related complications.

With regards to incidence of distant metastasis, Zaheer, Pemberton et al found Liver as the most commonly involved organ & 11.2% (19/169 patients) incidence of distant metastasis. Whereas Luna, Perz et al quoted an incidence of distant metastasis of 25.7% (35/137) in their patients. In our study, the incidence of distant metastasis after APR was 11% and liver was the most commonly

involved organ (Table – 3) . The local disease recurrence rates reported by McFarlane 10 et al after APR was 22% and that by Braun et al 21%. Our incidence of local disease recurrence was 23%. Hence, APR was found to be associated with significant local recurrence rates, which contributed to both morbidity and mortality.

In conclusion, Abdominoperineal resection (APR) carries low post operative mortality rate but a significant morbidity rate with respect to both immediate and delayed complications. The incidence of disease recurrence after APR is comparable with sphincter saving procedures. During the last two decades, low anterior resection with colo-anal or colo-rectal anastomosis has replaced APR as the primary surgical therapy for rectal cancer and the concept of Total Mesorectal Excision (TME) has become the standard of care for this malignancy. But despite these recent trends, to quote Murray and Veidenheimer, “APR remains the gold standard to which all other operations must be compared for all cancers of the lower thirds and for bulky tumors of the middle third of rectum”.

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## Ancient India

Indian physician Sushruta (c. 600 BC) taught and practiced surgery on the banks of the Ganges, now Benares in Northern India. Sushruta is a series of volumes he authored, known as the *Susrutha Samhita*. It is the oldest known surgical text and it describes in exquisite detail the examination, diagnosis, treatment, and prognosis of numerous ailments, as well as procedures on performing plastic surgery, i.e. cosmetic surgery and rhinoplasty. In the Sushruta school, the first person to expound Âyurvedic knowledge was Dhanvantari who then taught it to Divodasa who, in turn, taught it to Sushruta, Aupadhenava, Aurabhra, Paushakalâvata, Gopurarakshita, and Bhoja. He is also known by the title “Father of Surgery.” The Samhita has some writings that date as late as the 1st century, and some scholars believe that there were contributions and additions to his teachings from generations of his students and disciples. Susrutha is also the father of Plastic Surgery and Cosmetic Surgery since his technique of forehead flap rhinoplasty, that he used to reconstruct noses that were amputated as a punishment for crimes, is practiced almost unchanged in technique to this day. This knowledge of plastic surgery existed in India up to the late 18th century as can be seen from the reports published in Gentleman’s Magazine (October 1794). The Susrutha Samhita contains the first known description of several operations, including the uniting of bowel, the removal of the prostate gland, the removal of cataract lenses and the draining of abscesses. Susrutha was also the first surgeon to advocate the practice of operations on inanimate objects such as watermelons, clay pots and reeds; thus predating the modern practice of the surgical workshop by half a millennium.

# Inflammatory Bowel Disease

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**I**t is a nonspecific inflammatory disease of unknown aetiology, affecting the bowel. A number of other conditions which are associated with inflammation of the bowel are – Bacterial Colitis; Parasitic Colitis; Radiation Colitis; Ischemic Colitis. Unless the cause of Ulcerative Colitis and Crohn's disease are not known the term inflammatory bowel disease serves a useful purpose to distinguish these conditions from other bowel disorders. It is most commonly seen in the age group of 15 to 25 years, however a second peak in the incidence of IBD is seen at 60 to 70 years age. About 15 % of patients suffering from IBD have a close relative who also have IBD.

**Ulcerative colitis-** It is a nonspecific inflammatory disease of unknown aetiology affecting the large bowel. It is seen in both sexes and at any age but mostly affecting the second to fourth decades of life. Auto immunity, allergy to milk protein and genetic factors mostly predisposes to aetiological factors.

**Clinical features-** The severity varies from mild inflammation of mucosa to fulminating ulceration of colonic mucosa. The disease shows exacerbation and remission of varying intervals. It affects the variable part of large bowel, as proctitis, proctosigmoiditis, left sided colitis and pancolitis. The disease does not involve the small intestine but at times reactionary inflammatory changes are seen in terminal ileum which is called as back-wash ileitis. In mild case it may present with increased frequency of

stools. In severe cases massive diarrhoea, bleeding PR, tenesmus, abdominal cramps and fever are present. The predominant symptoms are bloody stools and diarrhoea. The severity of bleeding is in proportion to the stage of the disease, and nocturnal diarrhoea is frequent. Signs are minimal and nonspecific in mild cases. In severe cases abdominal tenderness, abdominal distension, fever, tachycardia, raised TLC are present. Bad prognosis is indicated by - a sudden and severe initial attack; disease involving the whole of colon; increasing age especially after 60 years. Prognosis is good if disease involves the left half of colon.

**Pathology-** Microscopically acute and chronic inflammatory response is seen in the mucosa and submucosa with ulceration and regeneration. Multiple crypt abscesses are seen. During remission phase acute response is absent. The mucosa is atrophic, reduced goblet cells, crypts are distorted, submucosa thickened. Other coats are not involved and the inflammatory lesions are limited to mucosa and sub-mucosa. The mucosa becomes swollen, friable, which leads to ulceration, which involves the full thickness of mucosa. In early stage small ulcers are present on mucosa, which later coalesce to give extensive denudation. Secondary infection occurs on these denuded areas. In chronic stage the disease starts in rectum leading to proctitis, later it extends proximally to involve the sigmoid colon, descending colon - proctosigmoiditis – left half colitis. In severe cases pancolitis results. The

episode of ulceration leaves behind island of mucosa which regenerates in chronic case to form polyp like structures which are called pseudopolyps. In severe fulminating cases the wall of colon becomes thinned out, specially seen in transverse colon, which become dilated leading to toxic megacolon, at this stage the colon may perforate, resulting in perforation peritonitis.

**Malignant changes-** Frequency of malignant change in ulcerative colitis is high. The high risk factors include - childhood onset; pancolitis; duration of disease is more than 10 years.

**Investigations -Proctoscopy -** Loss of normal vascular pattern of mucosa due to mucosal edema. Mucosa shows edematous, inflamed, granularity and friability. Ulceration and bleeding points. Fine granularity is seen in acute cases and coarse granularity is seen in chronic disease. Biopsy in acute stage shows nonspecific inflammatory changes and is not diagnostic.

**Colonoscopy and biopsy-** This is done to - establish the extent of disease; distinguish between Ulcerative Colitis and Crohn's Disease; monitor the response of treatment; multiple biopsies are taken to know the dysplastic changes in diseases which are more than 10 years duration.

**Barium enema-** This shows loss of haustrations specially in distal colon; mucosal changes due to granularity; pseudopolyps; in chronic cases a narrow and contracted colon; in Chronic cases

colonic stricture may be seen. (Colonic stricture in Ulcerative colitis should be taken as malignancy unless proved otherwise.) If the disease is more than 10 years old annual colonoscopy is to be done even if the disease is quiescent to rule out malignant changes.

### **Extraintestinal manifestation-**

These could be as arthritis; skin lesions (Pyoderma gangrenosa); clubbing of fingers; Iritis; Liver disease (Sclerosing Cholangitis); Bile duct malignancy.

### **Medical treatment**

**Diet and nutrition** - Patients with mild attack of IBD are able to take food orally. Fibres are restricted during active symptoms. Patient with Crohn's Disease have terminal ileal involvement and steatorrhea. These patient with Crohn's disease require fat soluble vitamin supplementation. Parenteral B12 supplementation. Iron replacement. In severe IBD patient are nil by mouth and require TPN.

**Drugs-** Sulphasalazine & aminosalicylates are the most commonly used drugs in IBD It has been shown to be effective in the treatment of active as well as remitted case of ulcerative colitis and Crohn's disease, when colon is involved. The drug sulfasalazine consists of two drugs, a Sulfapyridine and a 5 Aminosalicylic acid (5 ASA) which are linked by azobond. Intestinal bacteria breaks the azobond and release the 2 components. The sulfapyridine is systemically absorbed and is excreted in the urine. The active component 5 ASA is not absorbed and remains in the gut lumen in contact with the mucosa and is excreted with the stools.. Side effect - Abdominal discomfort, it is due to the effect of salicylates on the upper GI tract. This problem can be minimised by giving Sulfasalazine with

meals. Sulfasalazine competes with folates for absorption so patients become folate deficient. Other side effect are skin eruption, bone marrow depression is due to sulfapyridine part. Dosage: The initial daily dose is low (1 Gm) to minimize GI side effects. A therapeutic dose of 3 to 4 Gms per is appropriate. CBC and liver chemistry is done every 3 months initially then every 6 months in the long term treatment. Maintenance treatment of 2 to 3 Gms per day in divided dose has been shown to reduce the frequency of exacerbations of ulcerative colitis.

**Other 5 ASA Preparations-** The side effect of sulfasalazine is due to the Sulfapyridine part of the drug. So the interest is to develop a drug which has the salicylate part but not the sulfapyridine part. Several oral 5ASA preparations are available, Olsalazine which consists of two 5ASA molecules joined by an azobond and which require bacterial degradation in the colon to release the 2 molecules of 5ASA. Asacol and Pentasa are controlled release tablets of 5ASA. Balsalazine is a newer 5ASA preparation which is effective in the treatment of IBD involving left sided colon. Topical 5ASA preparations are Mesacol enema and Mesacol suppositories. 5ASA preparations are also recommended in patients with Crohn's disease to prevent post operative recurrence.

**Corticosteroids-** Corticosteroids has been used in the treatment of severe ulcerative colitis and Crohn's disease to reduce remission. IV Hydrocortisone 100 to 200 Mgs 6 hourly is used. Or Methylprednisolone in the dose of 10 to 20 Mgs IV 6 hourly are usually used in such patients. When patients can take oral medicines, prednisolone tablets in a dose of 40 to 60 Mgs per day usually given for 3 to 4 weeks. When symptoms improves

the drug is tapered off in several months. Steroids are not recommended for maintenance therapy of Ulcerative colitis and Crohn's disease because steroids do not prevent relapse of UC and Crohn's disease and they have major side effects. Many patient become Steroid dependent when recurrence of symptoms occur when dose of steroids are reduced. In such cases one strategy is to use immunomodulators such as Azathioprim, 6 Mercaptopurine, Methotrixate, Cyclosporin, in steroid dependent patients to help taper the dose of steroids, second option is Surgery. Corticosteroid enemas are also available for the treatment of proctitis and distal colitis.

**Antibiotics-** Most patients with mild to moderate IBD are successfully treated by Sulfasalazine or 5ASA and occasionally may require systemic or topical steroids therapy to treat disease relapse. However 20 to 30 % of patients with Ulcerative colitis and 30% of patients with Crohn's disease require additional therapy for refractory disease. Bacteria is known to play an important role in the pathogenesis of Crohn's disease and Ulcerative colitis. In Crohn's disease antibiotics are used to treat perianal abscesses and fistula, microperforation, localized peritonitis, bacterial overgrowth in chronic stricture. Antibiotics should be considered in patients not responding to 5ASA preparations prior to initiating steroid therapy.

**Metronidazole-** Has been shown to be effective in patients with Crohn's disease of the colon of combined small bowel and large bowel disease, and in perirectal and fistulizing Crohn's, some patient with Ulcerative colitis also responds to Metronidazole.

**Ciprofloxacin**- Useful in patients with colonic Crohn's and in perirectal and fistulising Crohn.

**Combination of Metronidazole and Ciprofloxacin.**

**Indications of Immunomodulator Drugs**

Crohn's disease	Ulcerative Colitis
Refractory Crohn's	Refractory Ulcerative colitis
Steroid Dependent	Steroid Dependent
Remission & maintenance Crohn's	Remission & maintenance of UC
Fistulizing Crohn's	
Prevention of Post operative recurrence	

Immunomodulator Drugs are- Azathioprim, 6 Merkapto purine, Cyclosporin, Methotrixate, Infliximab. Infliximab is an antibody against Human Tumour Necrosis Factor -2. which play an important role in pathogenesis of Crohn's disease. Infliximab is effective in the treatment of moderate to severe active Crohn's disease and fistulising Crohn's. It may also be beneficial in severe active UC. Further studies are underway to see the long term use of Infliximab in IBD. It is advisable to continue the use of 5ASA, antibiotics, steroids and immunomodulator drugs, during and after the infusion of Infliximab.

**Nicotine** -In enema form has been shown beneficial in Ulcerative colitis.

**Anti-diarrhoeal drugs** - If diarrhoea does not improve with the above mentioned medical therapy the anti diarrhoeal drugs can be used. Codine is most effective. Imodium and Lomotil is used in mild to moderate IBD. In severe IBD they should not be used as they tend to precipitate toxic megacolon.

**Bile acid binding resins** - Because of patients with Crohn's disease have involvement of terminal ileum which results in bile acid malabsorption, diarrhoea, steatorrhoea. Treatment with bile acid binding resins are indicated such as Cholestyramine.

**Surgical management**

**Indication for Surgery** - Risk of colectomy is 20% in overall ranging from 5% in those patients with only proctitis to 50 % in those patients with severe attack of pancolitis.

- Severe fulminating disease failing to respond to medical therapy for 7 days.
- Chronic disease with anemia.
- Steroid dependent disease - Here the disease is not severe but remission cannot be maintained without substantial dose of steroids.
- Severe haemorrhage, stenosis, obstruction, perforation.
- Extraintestinal manifestations.

**Operations** - Total abdominal colectomy with end ileostomy, is done in emergency situation as a firstaid procedure. The restorative surgery is done at a later date ;when the patient is no longer on steroid and in optimal nutritional condition -Ileorectal or ileoanal anastomosis.

(2) Proctocolectomy with ileostomy. Restorative proctocolectomy with an ileoanal pouch anastomosis. J Pouch, S Pouch, W Pouch. Colectomy with ileorectal anastomosis when the rectum is minimally involved.

**Toxic megacolon and severe IBD** - Toxic megacolon ia a condition in which the colon becomes atonic and dilated because of transmural

inflammation. It is mostly associated with severe ulcerative colitis, but it may be associated with any severe inflammatory condition of the bowel- Crohn's disease, Bacterial colitis, Parasitic colitis, Pseudomembranous colitis, Ischemic colitis, Radiation colitis. Some patient with severe ulcerative colitis do not have toxic megacolon but they require intensive treatment, because at any time toxic megacolon can be precipitated. Patient with toxic megacolon are seriously ill. They have fever, tachycardia, raised TLC, bloody diarrhoea and sepsis.

**Pathogenesis** - In most instances of colitis inflammatory process is confined to the mucosa and submucosa. Toxic megacolon develops as a result of the extension of the inflammatory process to the muscularis mucosa and serosa, leading to peritonitis and some times perforation. Several factors predisposes to the development of toxic megacolon

- Reduction in the medication of IBD.
- Hypokalemia causing paralytic ileus.
- Narcotics.
- Anticholenergic drugs.
- Drugs which dimnish bowel movements.
- Cessation of smoaking in patient with Ulcerative Colitis.

Bowel stasis facilitates extension of inflammatory process. The sign and symptoms are - At initial stages there is worsening of diarrhoea (more than 6 stools per day), fever, techycardia, abdominal tenderness, abdominal distension. As the disease progress the stool frequency diminish and the colon become atonic and dilated. Physical



examination shows :

- Patient appear severely ill.
- Sign of systemic toxicity. Fever, tachycardia, change in mental status.
- Abdomen is diffusely tender.
- Abdomen is distended.
- Bowel sounds are absent.
- Sign of peritonitis.
- P/R shows bloody stools.

Severe case of ulcerative colitis are regarded as medical emergency and should be treated in hospital. Patient should be examined twice a day for signs of peritonitis. Abdominal girth is measured. Scout film abdomen is done daily to (a) see the diameter of transverse colon, a diameter more than 6 Cms are regarded as abnormal. (b) Perforation is common in toxic megacolon thus upright or lateral decubitus films should be taken to rule out free gas. Barium enema and Colonoscopy is contraindicated. Limited sigmoidoscopy by an experienced endoscopist is safe and indicated. The examination should be limited to rectum and distal sigmoid. The severity of mucosal injury is assessed. To know the other causes of severe colitis - Crohn's disease, Ischaemic colitis, pseudomembranous colitis, parasitic colitis.

### Management of toxic megacolon

**General management** - Nil by mouth; IV Fluids; RT aspiration; Opiates and anticholinergics should be stopped; Correct electrolyte imbalance; Correct anemia by blood transfusion.

**Antibiotics** - Should be treated with broad spectrum antibiotics, giving a good anaerobic coverage.

**Corticosteroids** - Hydrocortisone

given IV in the dose of 100 to 200 Mgs 6 hourly.

Cyclosporin and Azathioprim or 6 Merkeptopurine are started.

**Surgery** - Patients with severe Ulcerative Colitis or toxic megacolon should be treated by a surgeon early in the course of the disease. The indications of surgery are - perforation; unremitting colonic haemorrhage; failure of the clinical status to improve even after intensive treatment with IV Steroid in combination with Cyclosporin. If the patient does not improve within 7 days of this regimen should be subjected to surgery. Surgery is subtotal colectomy with ileostomy, is considered the conservative procedure of choice in patients with systemic toxicity. But in patients without systemic toxicity - Total proctocolectomy with ileoanal pouch anastomosis is possible.

**Crohn's disease** - It was first reported by Crohns in 1932. It can affect any part of gastrointestinal tract, from mouth to anal margin. but ileocecal involvement is the most common presentation. It is slightly more common in females than in males. It is seen in young patients of the age group of 25 to 40 years. But another peak of incidence is seen around the age group of 17 years. Although the Crohn's disease has some features suggestive of chronic infection but no definite causative organisms has been found till now. It differs from the Ulcerative colitis by its segmental involvement and it can affect any part of the gut.

**Aetiology** - Similarities between Crohn's disease and tuberculosis has focused attention on mycobacterium. Penetration of bowel mucosa by E.Coli was thought to set the inflammatory

process. Hereditary seems to play a strong role. Ulcerative colitis can affect the relatives of patients with Crohn's disease but not vice versa. About 10% of the patient with Crohn's disease have a first degree relative suffering with the disease. Focal ischaemia has been postulated as the causative factor, possibly originating from vasculitis arising from immunological process. Smoking increase the risk by 3 folds. Cell mediated immune function is defective in patients with Crohn's disease, but it is not known that it is due to the consequence of the disease or it is the effect of malnutrition and medical treatment. Crohn's disease can predispose to cancer although the incidence of malignant change is not so high as in ulcerative colitis.

**Pathology** - Ileal disease is most common, accounting for 60% of the cases, 30% of the cases are limited to large bowel.. Anal lesions are common, but Crohn's disease of the mouth, oesophagus, stomach and duodenum are uncommon. Resected specimen shows fibrotic thickening of small bowel wall with narrowed lumen. The bowel proximal to the stricture is dilated. The mucosa shows linear or snake like deep mucosal ulcers. Oedema of the mucosa between the ulcers give a cobble stone appearance. There is transmural extension of the inflammation giving rise to adhesion, mesenteric abscesses, fistula, into the adjacent organs. Serosa is opaque and mesentery is thickened with enlarged mesenteric lymph nodes. Similar lesions may be present proximally but the condition is discontinuous with the other inflamed area being separated with normal intestine. These are called as skip lesion. Microscopically - there are focal areas of chronic inflammation involving all the layers of the intestinal wall. There are noncaseating giant cell granulomas

most commonly seen in the lesions of anorectal disease. The earliest mucosal lesions are the aphthous ulcers. Recent studies have shown multifocal arterial occlusion in muscularis propria.

**Clinical features** - Presentation depend on the area of involvement. The disease has an insidious onset of pain in abdomen, anemia, hypoproteinemia. Acute Crohn's disease occurs in 5% of cases. Sign and symptoms resembles that of Acute Appendicitis. But there is diarrhoea preceding the attack. Rarely there is perforation of small intestine resulting in local or diffused peritonitis. Acute colitis with or without toxic megacolon can occur in Crohn's disease but it is less common than in ulcerative colitis. In chronic Crohn's disease there is often history of mild diarrhoea which is accompanied by intestinal colic since many months. Patient complains of pain in right iliac fossa, there may be tender mass palpable. Intermittent fever, anemia, hypoproteinemia, weight loss are common. Perianal abscess and fissure may be the first presenting feature in Crohn's disease. The cause is infected anal crypts due to diarrhoea. As the disease become chronic fistulae develops due to Crohn's disease itself. (1) Entero-enteric Fistula. (2) Entero-colic Fistula (3) Entero-vesical Fistula which may cause recurrent urinary tract infection and pneumaturia. (4) Entero-cutaneous Fistula is rare but may develop following surgery.

### Investigations

**Sigmoidoscopic examination** - It is normal but ulceration in anal canal may be seen.

**Colonoscopy** - Rectal mucosa is normal in patients who have Crohn's disease without rectal involvement. Rectal Crohn's shows patchy

involvement. The mucosal edema, deep linear ulcers and fibrosis are the features of chronic disease. A rare variety with involvement of colon and rectum in continuity with granular and friable mucosa is extremely difficult to differentiate from Ulcerative colitis, unless Histopathological examination is done which shows giant cells in Crohn's disease.

**Radiology - Barium meal & follow through**, the characteristic features are - (a) Skip lesion. (b) Ironed out Valvulae Conniventes. (c) Absence of peristalsis and lead pipe like segments. (d) Longitudinal and transverse fissures projecting outside in the bowel wall giving cobble stone mucosal pattern. (e) Constriction of terminal ileum, narrow stricture. When longer length of ileum is involved then **string sign of Kantor** is seen. (f) Dilatation of proximal ileum. **Sinogram**- In enterocutaneous fistula. **CT Scan** for intraabdominal abscesses.

**Differentiation from ulcerative colitis**- The following features differentiate Crohn's disease from UC - severity of pain, intestinal colicky pain of Crohn's disease; absence of blood in stools; palpable mass; Intestinal Obstruction; small bowel involvement; Fistulae and perianal abscess in rectal and anal involvement; segmental pattern of involvement; aphthous linear ulcers; full thickness involvement of bowel wall; Sarcoid type of giant cells in H P R. Preoperative differentiation is important as Total Proctocolectomy, as done in ulcerative colitis will not eradicate the disease.

### Management

#### Medical therapy

Mild to moderate type of cases are treated on outpatient basis. But severe

symptomatic cases require hospitalisation. The drug of choice is Sulfasalazine. Starting with 1Gm daily and increasing to 4 Gms daily until total remission is achieved then the drug is tapered off. Low dose Metronidazole is also effective. Prednisolone at a dose of 60 Mgs per day in 3 to 4 divided dose for 10 to 14 days then tapered off. Immunosuppressive agents - Azathioprim, 6Merkaptopurine.

#### Surgical therapy

It is indicated in (a) Recurrent Obstruction. (b) Perforation. (c) Adhesion and obstruction. (d) Intestinal fistula. (e) Perianal disease. (f) Failure of medical treatment. (g) Malignant changes. Surgical resection will not cure the Crohn's Disease. So surgery should be limited to treatment of complication of the disease. Because by removing a segment of diseased bowel does not cure the patient of Crohn's disease as proctocolectomy cures a patient of Ulcerative Colitis. The aim of the surgical treatment is to remove as little bowel as it is necessary to correct the problem. Patients with single, short segment of Crohn's disease responds best to surgery. Ileocolic anastomosis of a patient having had previous ileocaecal resection for Crohn's disease, recurrent disease is seen on the ileal side of the anastomosis. Strictureplasty is the surgical option in stricturing Crohn disease. Recurrence rate after surgery is high- 30% after 5 Years, 50% after 10 Years and 70% after 15 Years. The aim of surgery is to remove grossly diseased bowel and to preserve as much normal appearing bowel as possible. If terminal ileum is removed patient should be investigated for B 12 deficiency every 6 months. Most patient will require B 12 injection every month.

### Differentiation of Ulcerative Colitis From Crohn's Disease

	Ulcerative Colitis	Crohn's Disease
Site of disease	Colon only	Any part of GI Tract
Distribution	Diffused	Focal (Segmental) skip areas
Anatomical plane	Mucosa & Submucosa	Transmural
Colonic appearance	Diffused friability	Focal/Apthous ulcers Cobble stone appearance. Linear ulcers with normal surrounding mucosa
Histopathology		
Crypt architecture	Distorted (crypt abscess)	Normal or focally distorted
Inflammation	Acute & Chronic	Normal or acute/chronic
Epithelioid granulomas	Never	Present
Complications	Internal fistulae/abscess never or rarely occurs	Fistulae & abscess can occur
Strictures	Uncommon	Common
Cancer risk after long standing disease	+ + + +	+ +

#### Development of Surgery in different regions

##### Ancient China

**H**ua Tuo was a famous Chinese physician during the Eastern Han and Three Kingdoms era. He was the first person to perform surgery with the aid of anesthesia, some 1600 years before the practice was adopted by Europeans.

##### Medieval Europe

Abulcasis (Abu al-Qasim Khalaf ibn al-Abbas Al-Zahrawi) was an Andalusian-Arab physician and scientist who practised in the Zahra suburb of Cordova. He is considered a great medieval surgeon, whose comprehensive medical texts, combining Middle Eastern and Greco-Roman classical teachings, shaped European surgical procedures

up until the Renaissance. He is often regarded as the Father of Surgery. Patients and students from all parts of Europe came to him for treatment and advice. According to Will Durant, Cordova was in this period the favourite resort of Europeans for surgical operations.

##### Surgery in Holland (ca. 1690)

By the 13th century, many European towns were demanding that physicians have several years of study or training before they could practice. Montpellier, Padua and Bologna Universities were particularly interested in the academic side to Surgery, and by the 15th century at the latest, Surgery was a separate university subject to Physics. Surgery had a lower status than pure medicine, beginning as a craft tradition until Rogerius Salernitanus composed his

*Chirurgia*, which laid the foundation for the species of the occidental surgical manuals, influencing them up to modern times.

##### Europe

Ambroise Paré pioneered the treatment of wounds by gunshots. Among the first modern surgeons were battlefield doctors in the Napoleonic Wars who were primarily concerned with amputation. Naval surgeons were often barber surgeons, who combined surgery with their main jobs as barbers.

In London, an operating theatre or operating room from the day before modern anaesthesia or antiseptic surgery still exists, and is open to the public. It is found in the roof space of St Thomas Church, Southwark, London and is called the Old Operating Theatre.

## Renal Cancer

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**R**enal cell carcinoma accounts for approximately 3% of adult malignancies and 85-90% of neoplasms arising from the kidney. It is characterized by a lack of early warning signs, diverse clinical manifestations, resistance to radiation and chemotherapy, and infrequent but reproducible responses to immunotherapy agents such as interferon alpha & interleukin (IL)-2.

**Pathophysiology-** The tissue of origin for renal cell carcinoma is the proximal renal tubular epithelium. Renal cancer occurs in both a sporadic (nonhereditary) and a hereditary form, and both forms are associated with structural alterations of the short arm of chromosome 3 (3p). Genetic studies of the families at high risk for developing renal cancer led to the cloning of genes whose alteration results in tumor formation. These genes are either tumor suppressors (*VHL*, *TSC*) or oncogenes (*MET*). Smoking predisposes to renal cancer and smokers develop this cancer twice as often as non smokers.

**Mortality/Morbidity-** Renal cell carcinoma is the sixth leading cause of cancer death. The 5-year survival rates initially reported by Robson in 1969 were 66% for stage I renal carcinoma, 64% for stage II, 42% for stage III, and only 11% for stage IV. Except for stage I, these survival statistics have remained essentially unchanged for several decades.

**Race-** Renal cell carcinoma is more common in people of Northern European ancestry (Scandinavians) and

North Americans than in those of Asian or African descent. In India the incidence is 1.4% of all cancers.

**Sex-** Renal cell carcinoma is twice as common in men as in women. The male-to-female ratio is 2:1.

**Age-** This condition occurs most commonly in the fourth to sixth decades of life, but the disease has been reported in younger people who belong to family clusters.

**Aetiology-** A number of cellular, environmental, genetic, and hormonal factors have been studied as possible causal factors for renal cell carcinoma. Eg smoking, obesity, occupational exposure to petroleum products, heavy metals, asbestos and solvents, renal transplantation with its associated immunosuppression and VHL disease.

**Imaging studies-** A large proportion of patients diagnosed with renal cancer have small tumors discovered incidentally on imaging studies. A number of diagnostic modalities are used to evaluate and stage renal masses.

Contrast-enhanced CT scanning has become the imaging procedure of choice for diagnosis and staging of renal cell cancer and has virtually replaced excretory urography and renal ultrasound. In most cases, CT imaging can differentiate cystic masses from solid masses and supplies information about lymph node, renal vein, and inferior vena cava involvement.

**Histology-** Renal cell carcinoma has 5 histologic subtypes, as follows: clear cell

(75%), chromophilic (15%), chromophobic (5%), oncocytoma (3%), and collecting duct (2%).

**Staging-** The tumor, nodes, and metastases (TNM) classification is endorsed by the American Joint Committee on Cancer (AJCC). The major advantage of the TNM system is that it clearly differentiates individuals with tumor thrombi from those with local nodal disease. The TNM classification system is as follows:

- Primary tumor (T)
- TX - Primary tumor cannot be assessed
- T0 - No evidence of primary tumor
- T1 - Tumor 7 cm or smaller in greatest dimension, limited to the kidney
- T2 - Tumor larger than 7 cm in greatest dimension, limited to the kidney
- T3a - Tumor invades adrenal gland or perinephric tissues but not beyond the Gerota fascia
- T3b - Tumor grossly extends into the renal vein(s) or vena cava below the diaphragm
- T3c - Tumor grossly extends into the renal vein(s) or vena cava above the diaphragm
- T4 - Tumor invading beyond the Gerota fascia
- Regional lymph nodes (N) - Laterality does not affect the N classification
- NX - Regional lymph nodes cannot

be assessed

- N0 - No regional lymph node metastasis
- N1 - Metastasis in a single regional lymph node
- N2 - Metastasis in more than 1 regional lymph node
- Distant metastasis (M)
- MX - Distant metastasis cannot be assessed
- M0 - No distant metastasis, M1 - Distant metastasis
- AJCC Stages
- stage I - T1, N0, M0
- stage II - T2, N0, M0
- stage III - T1-2, N1, M0 or T3a-c, N0-1, M0
- stage IV - T4; or any T, N2, M0; or any T, any N, M1

### Treatment

More than 50% of patients with renal cell carcinoma are cured in early stages, but outcome for stage IV disease is poor. The probability of cure is related directly to the stage or degree of tumor dissemination, so the approach is curative for early stage disease. Selected patients with metastatic disease respond to immunotherapy, but many patients can be offered only palliative therapy for advanced disease. The treatment options for renal cell cancer are surgery, radiation therapy, chemotherapy, hormonal therapy, immunotherapy, or combinations of these.

**Surgery-** Surgical resection remains the only known effective treatment for localized renal cell carcinoma, and it also is used for palliation in metastatic disease.

- Radical nephrectomy, which remains the most commonly performed standard surgical

procedure today for treatment of localized renal carcinoma, involves complete removal of the Gerota fascia and its contents, including a resection of kidney, perirenal fat, and ipsilateral adrenal gland, with or without ipsilateral lymph node dissection. Radical nephrectomy provides a better surgical margin than simple removal of the kidney, since perinephric fat may be involved in some patients. Lymph nodes may be involved in 10-25% of patients. Regional lymphadenectomy adds little in terms of operative time or risk and should be included in conjunction with radical nephrectomy.

- Palliative nephrectomy should be considered in patients with metastatic disease for alleviation of symptoms such as pain, hemorrhage, malaise, hypercalcemia, erythrocytosis, or hypertension.

**Chemotherapy** and endocrine-based approaches are limited, and no chemotherapeutic regimen is accepted as a standard of care. Objective response rates, either for single or combination chemotherapy, usually are lower than 15%. Therefore, various biologic therapies have been evaluated.

Renal cell carcinoma is an immunogenic tumor, and spontaneous regressions have been documented. Many immune modulators, such as interferon, IL-2 (aldesleukin [Proleukin]), bacillus Calmette-Guérin (BCG) vaccination, lymphokine-activated killer (LAK) cells plus IL-2, tumor-infiltrating lymphocytes, and nonmyeloablative allogeneic peripheral blood stem-cell transplantation, have been tried.

**Multi-kinase inhibitors-** Future treatment strategies for advanced renal

cell carcinoma will likely incorporate a combination of molecular approaches, using multidrug regimens consisting of small molecule kinase inhibitors with biologic therapies and/or immunomodulatory therapies. *Sorafenib* (Nexavar) — First oral multikinase inhibitor that targets serine/threonine and tyrosine receptor kinases involved in tumor cell proliferation and angiogenesis, thereby decreasing tumor cell proliferation. These kinases included RAF kinase, VEGFR-2, VEGFR-3, PDGFR-beta, KIT, and FLT-3. Indicated for advanced renal cell carcinoma. Dose in adults is 400 mg PO bid 1 h ac or 2 h pc. Common adverse reactions include hand or foot skin reaction and rash (modify dose); may increase risk of hemorrhage, cardiac ischemia and/or infarction, alopecia, pruritus, or diarrhea. Another drug used is *Sunitinib* (Sutent) — Multikinase inhibitor that targets several tyrosine kinase inhibitors implicated in tumor growth, pathologic angiogenesis, and metastatic progression. Inhibits platelet-derived growth factor receptors (ie, PDGFR-alpha, PDGFR-beta), vascular endothelial growth factor receptors (ie, VEGFR1, VEGFR2, VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony-stimulating factor receptor type 1 (CSF-1R), and the glial cell-line-derived neurotrophilic factor receptor (RET). Indicated for advanced renal cell carcinoma. Reduces tumor size in patients with metastatic kidney cancer whose tumors have progressed following cytokine-based therapy. Standard dose: 50 mg PO qid on a schedule of 4 week on treatment followed by 2 week off treatment.

**Chemotherapy-** Renal cell carcinoma is refractory to most chemotherapeutic agents because of multidrug resistance mediated by *p*-glycoprotein. Normal

renal proximal tubules and renal cell carcinoma both express high levels of *p*-glycoprotein. Calcium channel blockers or other drugs that interfere with the function of *p*-glycoprotein can diminish resistance to vinblastine and anthracycline in human renal cell carcinoma cell lines.

**Biologic therapies-** The interferons are natural glycoproteins with antiviral, antiproliferative, and immunomodulatory properties. The interferons have a direct antiproliferative effect on renal tumor cells *in vitro*, stimulate host mononuclear cells, and enhance expression of major histocompatibility complex molecules. Interferon-alpha, which is derived from leukocytes, has an objective response rate of approximately 15% (range 0-29%).

Preclinical studies have shown synergy between interferons and cytotoxic drugs. In several prospective randomized trials, combinations do not appear to provide major advantages over single-agent therapy. Many different types and preparations of interferons have been used without any difference in efficacy.

IL-2 is a T-cell growth factor and activator of T cells and natural killer cells. IL-2 affects tumor growth by activating lymphoid cells *in vivo* without affecting tumor proliferation directly.

In the initial study by the National Cancer Institute, bolus intravenous infusions of high-dose IL-2 combined with LAK cells produced objective response rates of 33%. In subsequent multicenter trials, the response rate was 16%. Subsequent studies also showed that LAK cells add no definite therapeutic benefit and can be eliminated from the treatment. A high-dose regimen (600,000-720,000 IU/kg q8h for a maximum of 14 doses) resulted in a 19% response rate

with 5% complete responses. The majority of responses to IL-2 were durable, with median response duration of 20 months. Eighty percent of patients who responded completely to therapy with IL-2 were alive at 10 years. Most patients responded after the first cycle, and those who did not respond after the second cycle did not respond to any further treatment. Therefore, the current recommendation is to continue treatment with high-dose IL-2 to best response (up to 6 cycles) or until toxic effects become intolerable. Treatment should be discontinued after 2 cycles if the patient has had no regression. Combinations of IL-2 and interferon or other chemotherapeutic agents such as 5-FU have not been shown to be more effective than high-dose IL-2 alone.

Toxic effects associated with high-dose IL-2 are related to increased vascular permeability and secondary cytokine secretion (eg, IL-1, interferon gamma, tumor necrosis factor, nitric oxide). The management of high-dose IL-2 toxicities requires inpatient monitoring, often in an intensive care unit. The major toxic effect of high-dose IL-2 is a sepsis-like syndrome, which includes a progressive decrease in systemic vascular resistance and an associated decrease in intravascular volume due to capillary leak. Other toxic effects are fever, chills, fatigue, infection, and hypotension. High-dose IL-2 has been associated with a 1-4% incidence of treatment-related death and should be offered only to patients with no cardiac ischemia or significant impairment of renal or pulmonary functions. Management includes judicious use of fluids and vasopressor support to maintain blood pressure and intravascular volume and at the same time to avoid pulmonary toxicity due to noncardiogenic pulmonary edema from

the capillary leak. This syndrome is normally reversible.

**Radiation therapy** may be considered for palliation in patients whose clinical condition precludes surgery, either because of extensive disease or poor overall condition. A dose of 4500 centigray (cGy) is delivered, with consideration of a boost up to 5500 cGy. Preoperative radiation therapy yields no survival advantage.

Controversies exist concerning postoperative radiation therapy, but it may be considered in patients with perinephric fat extension, adrenal invasion, or involved margins. However there is no improvement in overall survival with adjuvant treatment in form of radiation or systemic therapy in non metastatic disease.

Palliative radiation therapy often is used for local or symptomatic metastatic disease, such as painful osseous lesions or brain metastasis, to halt potential neurological progression. Surgery also should be considered for solitary brain or spine lesions, followed by postoperative radiotherapy to the metastatic site.

About 11% of patients develop brain metastasis during the course of illness. Renal cell carcinoma is a radioresistant tumor, but radiation treatment of brain metastasis improves quality of life, local control, and overall survival duration. Patients with untreated brain metastasis have a median survival time of 1 month, which can be improved with glucocorticoid therapy and brain irradiation. Stereotactic radiosurgery is more effective than surgical extirpation for local control and can be performed on multiple lesions.

## Follow up after treatment

For stage I,II and II disease, complete history, physical examination, chest radiographs, liver function tests, BUN and creatinine, and calcium are recommended every 6 months for 2 years, then annually for 5 years. Abdominal CT scan is recommended once at 4-6 months and then as indicated.

Careful surveillance of patients with end-stage renal disease, VHL disease or renal transplant patients by ultrasonography and CT scan is recommended. Avoidance of causative factors such as smoking, obesity, and environmental carcinogens is recommended.

## Prognosis

Metastatic disease has increased survival with (1) a long disease-free interval between initial nephrectomy and the appearance of metastases, (2) the presence of only pulmonary metastases, (3) good performance status, and (4) removal of the primary tumor. Five-year survival rates are as follows:

The 5-year disease-specific survival rate associated with T1 renal carcinoma is 95% and with stage T2 disease, 88%. Patients with T3 renal carcinoma had a 5-year survival rate of 59%, and those with T4 disease had a 5-year disease-specific survival rate of 20%.

Patients with regional lymph node involvement or extracapsular extension have a survival rate of 12-25%. Although renal vein involvement does not have a markedly negative effect on prognosis, the 5-year survival rate for patients with stage IIIB renal cell carcinoma is 18%. In patients with effective surgical removal of the renal vein or inferior vena caval thrombus, the 5-year survival rate is 25-50%. Five-year survival rates for patients with stage IV disease are low (0-20%).

## Patient education

Patients in the high-risk group should be made aware of the early signs and symptoms, and the need for early intervention for possible cure should be stressed. Patients in early stages who have undergone treatment should be educated about possible relapse.

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### Development of modern surgery

To make its transition to the modern era the art of surgery had to overcome three major problems that were effectively

preventing surgery from progressing to become the widely respected discipline we see today. These three great barriers were, bleeding, infection & pain

#### Bleeding

There was a very real threat that a patient would bleed out on the table during an operation or bleed to death while being attended after an accident or wound. The first real progress in combating bleeding had come when early cultures realized they could close wounds using extremes of heat, a procedure called cauterizing. The early cauterization was successful, but only useable in a limited fashion, highly destructive, and painful, with terrible long term outcomes. The next real breakthrough to come was the invention of ligatures, something widely believed to have originated with Ambrose Pare during the 16th century. A ligature is a piece of material used to tie closed the end of a cut blood vessel preventing any further bleeding by serving to occlude it. Ligatures form the basis of modern control bleeding, but at the time, they were more of a hazard than a help because the surgeons using them had no concept of infection control. A final barrier to be overcome was the problem of replacing blood lost. Limiting bleeding is important, but ultimately, a surgeon is fighting a losing battle if blood cannot be replaced, and this final barrier was only conquered when early 20th century research into blood groups allowed the first effective blood transfusions.

#### Infection

Big holes into sealed internal environments lead to infections, especially if the surgeon is using unsterilised tools, covered in blood and wearing his normal clothes. The first progress in combating infection was made by the Hungarian doctor Semmelweiss who noticed that medical students fresh from the dissecting room were causing excess maternal death compared to midwives. Semmelweiss, despite ridicule and opposition,

introduced compulsory handwashing for everyone entering the maternal wards and was rewarded with a plunge in maternal and fetal deaths. Lister was able to quickly improve infection rates no end, a process that was further helped by his subsequent introduction of techniques to sterilise equipment, have rigorous hand washing and a later implementation of rubber gloves. Lister published his work as a series of articles in *The Lancet* (March 1867) under the title "Antiseptic Principle of the Practice of Surgery". The gradual development of germ theory has allowed the final step to be taken to create the highest quality of aseptic conditions in modern hospitals and this has allowed us to (theoretically) perform infection free surgery.

#### Pain

Before the advent of anesthesia (discovered by 2 American dentists, Horace Wells (1815-1848) & William Morton), surgery was a traumatically painful procedure and surgeons were encouraged to be as swift as possible to minimize patient suffering. This also meant that operations were largely restricted to amputations and external growth removals. Beginning in the 1840s, surgery began to change dramatically in character with the discovery of effective and practical anaesthetic chemicals such as ether and chloroform

#### Doctor or Mister?

In the UK, Australia, South Africa and New Zealand surgeons are distinguished from physicians by being referred to as "Mister." This tradition has its origins in the 18th century, when surgeons were barber-surgeons and did not have a degree, unlike physicians having medical degree. By the beginning of the 19th century, surgeons had obtained high status, and in 1800, the Royal College of Surgeons (RCS) in London began to offer surgeons a formal status via RCS membership. The title *Mister* became a badge of honour.



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Review  
article

Despite major advances in techniques for the management of ventilator-dependent patients and the routine use of effective procedures to disinfect respiratory equipment, ventilator-associated pneumonia (VAP) continues to complicate the course of 8 to 28% of the patients receiving mechanical ventilation (MV)<sup>1</sup>. Prolonged (more than 48 hours) MV is the most important factor associated with nosocomial pneumonia. However, VAP may occur within the first 48 hours after intubation. Rates of pneumonia are considerably higher among patients hospitalized in intensive care units (ICUs) compared with those in hospital wards, and the risk of pneumonia is increased 3- to 10-fold for the intubated patient receiving MV<sup>2</sup>. Because several studies have shown that appropriate antimicrobial treatment of patients with VAP significantly improves outcome, more rapid identification of infected patients and accurate selection of antimicrobial agents represent important clinical goals<sup>3</sup>. However, consensus on appropriate diagnostic, therapeutic, and preventive strategies for VAP has yet to be reached.

### Definition

VAP is defined as an inflammation of the lung parenchyma caused by infectious agents not present or incubating at the time MV was started. VAP refers to an infection of the lung parenchyma following intubations and MV for at least 48 hours.

### Classification and pathogenesis

VAP is typically categorized as either a) early-onset VAP (occurring in the first 3-4 days of mechanical ventilation) or b) late-onset VAP. This distinction is important microbiologically. Early-onset VAP is commonly caused by antibiotic-sensitive community-acquired organisms (e.g., *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus*). Late-onset VAP is commonly caused by antibiotic-resistant nosocomial organisms (e.g., *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus*, *Acinetobacter* species, and *Enterobacter* species). Pneumonia results from microbial invasion of the normally sterile lower respiratory tract and lung parenchyma caused by either a defect in host defenses, challenge by a particularly virulent microorganism, or an overwhelming inoculum. The normal human respiratory tract possesses a variety of defense mechanisms that protect the lung from infection, for example: anatomic barriers, such as the glottis and larynx; cough reflexes; tracheobronchial secretions; mucociliary lining; cell-mediated and humoral immunity; and a dual phagocytic system that involves both alveolar macrophages and neutrophils<sup>4</sup>. When these coordinated components function properly, invading microbes are eliminated and clinical disease is avoided, but when these defenses are impaired or if they are overcome by virtue of a high inoculum of organisms or organisms of unusual virulence, pneumonitis results. As suggested by the

infrequent association of VAP with bacteremia, the majority of these infections appear to result from aspiration of potential pathogens that have colonized the mucosal surfaces of the oropharyngeal airways. Intubation of the patient not only compromises the natural barrier between the oropharynx and trachea, but may also facilitate the entry of bacteria into the lung by pooling and leakage of contaminated secretions around the endotracheal tube cuff<sup>5</sup>. This phenomenon occurs in most intubated patients, whose supine position may facilitate its occurrence. In previously healthy, newly hospitalized patients, normal mouth flora or pathogens associated with community-acquired pneumonia may predominate. In sicker patients who have been hospitalized more than 5 days, GNB and *S. aureus* frequently colonize the upper airway<sup>6</sup>.

Other sources of pathogens causing VAP include the paranasal sinuses, dental plaque, and the subglottic area between the true vocal cords and the endotracheal tube cuff. The role of the gastrointestinal tract as a source of oropharyngeal and tracheal colonization by GNB is more controversial<sup>7</sup>. A sequence of events leading to colonization from the stomach to the trachea, with increasing frequency in direct correlation to the gastric pH, was reported by several investigators, with 27 to 45% of patients having primary colonization of the gastric juice and subsequent colonization of the tracheobronchial tree 2 days later<sup>8</sup>. Other studies have clearly proven, by means of radio-labeled gastric juice or

other techniques, that the gastric juice of intubated patients is aspirated into the tracheobronchial tract within a few hours<sup>9</sup>.

In fact, there is more than one potential pathway for colonization of the oropharynx and trachea in such a setting, including fecal-oral cross-infection on the hands of health care personnel, and contaminated respiratory therapy equipment. Patient care activities, such as bathing, oral care, tracheal suctioning, enteral feeding, and tube manipulations, provide ample opportunities for transmission of pathogens when infection control practices are substandard<sup>10</sup>.

In summary, the relationship between VAP and tracheal, pharyngeal, and/or gastric colonizations remains to be elucidated for patients with an endotracheal tube. To date, these findings lead to the following conclusions: (1) tracheal colonization precedes VAP in most, but not all, patients; (2) only a minority of patients with tracheal colonization develop VAP; (3) the stomach can be a reservoir for pneumonia pathogens, although this is not the case in many ICU patients requiring MV.

### Diagnosis

VAP can be accurately diagnosed by any one of several standard criteria: histopathologic examination of lung tissue obtained by open lung biopsy, rapid cavitation of a pulmonary infiltrate in the absence of cancer or tuberculosis, positive pleural fluid culture, same species with same antibiogram isolated from blood and respiratory secretions without another identifiable source of bacteremia, and histopathologic examination of lung tissue at autopsy<sup>11</sup>. However, these criteria are based on invasive procedures for obtaining lung tissue or on uncommon manifestations or

complications of VAP. Given the invasive nature of lung biopsy and the infrequent occurrence of other manifestations used as standard criteria, another approach is needed for the definitive diagnosis of VAP. In 1979, a fiberoptic bronchoscopic technique was introduced for obtaining uncontaminated lower respiratory tract secretions, which were cultured quantitatively<sup>12</sup>. Two bronchoscopic techniques have been introduced for the accurate diagnosis of VAP. The protected specimen brush (PSB) collects 0.001 mL of lower respiratory tract secretions and has a diagnostic threshold of  $\geq 10^3$  CFU/mL<sup>13</sup>. BAL, an unprotected technique, samples approximately one million alveoli and has a diagnostic threshold of  $\geq 10^4$  CFU/mL<sup>13</sup>. A protected BAL technique with a balloon-tipped catheter has also been described. Detection of  $\geq 5\%$  of neutrophils or macrophages with intracellular organisms on a Wright-Giemsa stain of a smear of cytocentrifuged BAL fluid is also diagnostic of VAP<sup>14</sup> (table)

Because of the invasive nature and cost of bronchoscopy, investigators have evaluated other techniques for collecting lower respiratory tract secretions. These non bronchoscopic techniques involve passage of a catheter or telescoping catheters through the endotracheal tube with advancement to a wedged position in the lung. Samples may be taken by telescoping catheters containing a brush (blind PSB)<sup>15</sup>, aspiration of secretions into a distally wedged catheter, or BAL through a distally wedged catheter. BAL may be performed by using a balloon-tipped catheter with the balloon inflated after the catheter has been advanced to the wedged position (protected BAL), by using telescoping catheters, or by placing a catheter into the wedged position with a guide wire. Despite broad clinical experience with the PSB and BAL techniques, it remains, nonetheless, unclear which one should be used in clinical practice. Their operating characteristics for diagnosing VAP are probably similar, with only small differences in their sensitivities and

Diagnostic techniques	Sensitivity	Specificity	Negative predictive value	Positive predictive value
PSB <sup>b</sup> cultures ( $\geq 10^3$ CFU/mL)	82%	89%	90%	89%
BAL cultures ( $\geq 10^4$ CFU/mL)	91%	78%	83%	87%
Microscopic examination of BAL fluid ( $\geq 5\%$ intracellular organisms)	91%	89%	91%	89%

<sup>a</sup>From ref 10.  
<sup>b</sup>PSB = protected specimen brush; BAL = bronchoalveolar lavage.

specificities. Most investigators prefer to use BAL rather than PSB to diagnose bacterial pneumonia, because BAL (1) has a slightly higher sensitivity to identify VAP-causative microorganisms, (2) enables better selection of an empiric antimicrobial treatment

before culture results are available, (3) is less dangerous for many critically ill patients, (4) is less costly, and (5) may provide useful clues for the diagnosis of other types of infections. However, it must be acknowledged that a small return on BAL may contain only diluted material from the bronchial rather than the alveolar level and thus give rise to false-negative results, particularly for patients with severe COPD. In these patients, the diagnostic value of BAL techniques is greatly diminished and the PSB technique should be preferred. Therefore, the choice of procedure(s) may eventually depend on the preferences and experiences of individual physicians and the patient's underlying disease(s).

VAP is more common in patients with ARDS than in those with other causes of respiratory failure<sup>16</sup>; it occurs later and is caused by more resistant microorganisms. The diagnosis of VAP is more difficult in such patients because ARDS and VAP have very similar clinical manifestations. Given the severity of illness of patients with ARDS, particularly when complicated by VAP, and the great difficulty in differentiating VAP from ARDS on clinical and radiographic grounds, the most effective approach to diagnosis of VAP in patients with ARDS is quantitative culture and microscopic examination of lower respiratory tract secretions.

### Treatment

Successful treatment of patients with VAP remains a difficult and complex undertaking for several reasons. First, the criteria for a definitive diagnosis of VAP in critically ill patients remain to be established. Although it is difficult to clinically distinguish between bacterial colonization of the tracheobronchial tree

and true nosocomial pneumonia, nearly all previous therapeutic investigations have relied solely on clinical diagnostic criteria and, therefore, have probably included patients who did not have pneumonia. Second, most of those studies used tracheal secretions as the major source of specimens for microbiologic cultures, despite the fact that the upper respiratory tract of most ventilated patients is usually colonized with multiple potential pathogens. Finally, the lack of an adequate technique to directly sample the infection site in the lung has hampered the study of the ability or inability of antibiotics to eradicate the causative pathogens from the lower respiratory tract and, therefore, to predict their bacteriologic efficacy.

### Antibiotics

Two factors appear to render the choice of antibiotics particularly difficult in critically ill patients. First, VAPs are likely to result from highly resistant organisms, especially in patients who were previously treated with antibiotics. Second, multiple organisms are frequently cultured from the pulmonary secretions of patients considered to have pneumonia. Because of the emergence of multiresistant, extended spectrum lactamase-producing GNB in many institutions and the increasing role played by gram-positive bacteria, such as MRSA, even a protocol combining ceftazidime or imipenem and amikacin would not ensure adequate coverage of all cases of VAP in these ICUs. Therefore, no "magic bullet" exists to cover all the microorganisms potentially responsible for VAP.

Core organisms responsible for ventilator-associated pneumonia and recommended antimicrobial therapy<sup>17</sup>

Core Organisms	Core
Antibiotics	
Early-onset VAP, no specific risk factor	
Enteric gram negative (nonpseudomonal)	Cephalosporin
<i>Enterobacter</i> spp.	Second generation
<i>Escherichia coli</i>	Nonpseudomonal 3rd generation
<i>Klebsiella</i> spp.	Or
<i>Proteus</i> spp.	Lactam-lactamase inhibitor combination
<i>Serratia marcescens</i>	
<i>Haemophilus influenzae</i>	If allergic to penicillin:
MSSA	Fluoroquinolone
	Or
<i>Streptococcus pneumoniae</i>	
Clindamycin + aztreonam	
Late-onset VAP	
Core organisms <i>plus</i> ciprofloxacin <i>plus</i> one of the following:	Aminoglycoside or
<i>Pseudomonas aeruginosa</i>	Antipseudomonal penicillin
<i>Acinetobacter baumannii</i> inhibitor	Lactam Lactamase combination Ceftazidime or cefoperazone Imipenem Aztreonam
Consider MRSA	± Vancomycin

Definition of abbreviations: MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-sensitive *S. aureus*; VAP = ventilator-associated pneumonia. Adapted from the American Thoracic Society (33).

Because the guidelines have not been updated since their publication in

1996, they do not include newer therapies (e.g., cefepime, meropenem, and newer fluoroquinolones) that may be effective and/or associated with less resistance.

### **Duration of antimicrobial therapy**

A “long” treatment, that is, a minimum of 14 to 21 days, is prescribed for the following situations: multilobar involvement, malnutrition, cavitation, gram-negative necrotizing pneumonia, and/or isolation of *P. aeruginosa* or *Acinetobacter* spp. This duration is essentially justified by the high theoretical risk of relapse. A “short” treatment, lasting 7 to 10 days, is recommended for *S. aureus* or *H. influenzae* pneumonia.

However, a regimen of insufficient duration can be the source of therapeutic failure or relapse, defined as the reappearance of signs of pneumonia and isolation of the same pathogen(s), which may or may not have acquired resistance. The risk is probably small for bacteria considered susceptible but might be high for certain strains, especially *P. aeruginosa* and MRSA, which are particularly difficult to eradicate from the respiratory tract<sup>18</sup>. This situation is even further aggravated in certain immunocompromised patients. Thus, at present, a short-term regimen is rarely prescribed, despite the potential major advantages it could have in terms of bacterial ecology, the prevention of the emergence of multiresistant bacteria, and, obviously, lower costs. Lowering the amount of antibiotics administered to patients in the ICU is indeed a primary objective of every strategy aimed at preventing the emergence and dissemination of such bacteria.

### **Prevention of Ventilator-**

### **Associated Pneumonia**

Four practices that carry the potential to reduce the incidence of VAP in patients receiving mechanical ventilation are:

**Patient positioning-** Semi-recumbent Positioning and Continuous Oscillation. Aspiration of gastric secretions likely contributes to the development of VAP. Semi-recumbent positioning of mechanically ventilated patients may help reduce the incidence of gastroesophageal reflux and lead to a decreased incidence of VAP. Semi-recumbent positioning is generally defined as elevation of the head of the bed to 45 degrees. This position should be avoided in the following conditions: recent abdominal or neurologic surgery (<7 days), shock refractory to vasoactive therapy, and previous recent endotracheal intubation (<30 days). **Oscillation -** Continuous oscillation utilizes mechanical beds that employ either rotating platforms or alternating inflation/deflation of mattress compartments to turn patients from side to side. These beds achieve 40 to 60 degrees of tilt and can cycle every 5-30 minutes as programmed.

**Continuous aspiration of subglottic secretions-** Tracheal intubation interrupts the body’s anatomic and physiologic defenses against aspiration, making mechanical ventilation a major risk factor for VAP. The accumulation of contaminated oropharyngeal secretions above the endotracheal tube cuff may contribute to the risk of aspiration. Removal of these pooled secretions through suctioning of the subglottic region, termed continuous aspiration of subglottic secretions (CASS), may reduce the risk of developing VAP.

**Selective digestive tract decontamination-** Selective digestive tract decontamination (SDD) involves the use of non-absorbable antibiotics topically applied to the gastrointestinal tract in an effort to sterilize the oropharynx and stomach. Most studies have used a combination of topical polymyxin, tobramycin or gentamicin, and amphotericin applied to the oropharynx (by hand) and the stomach (by nasogastric tube). About half of the studies also included a short (3-4 day) course of systemic intravenous antimicrobial therapy, most commonly ceftriaxone. In general, topical antibiotics were applied several times daily from the time of intubation until extubation (or shortly thereafter).

**Sucralfate and prevention of VAP-** It has been observed that gastric colonization by potentially pathogenic organisms increases with decreasing gastric acidity, leading to the hypothesis that pH-altering drugs may cause increased rates of VAP. H<sub>2</sub>-antagonist therapy, widely used in mechanically-ventilated patients for stress ulcer prophylaxis significantly elevates gastric pH. Sucralfate, an alternative prophylactic agent that does not affect gastric pH, may allow less gastric colonization with potentially pathogenic organisms than H<sub>2</sub>-antagonists and therefore prevent some cases of VAP. In general, 1 g of sucralfate suspension is given through a nasogastric tube every four to six hours.

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Review  
article

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**E**sophageal cancer is a challenging disease with a poor outlook and hence there is justification for a wide spread pessimism, that affects clinicians who manage these patients. In cancer of Esophagus not every patient has a bad prognosis and there are many, whose disease can be cured, and for those who are incurable, methods of palliation continue to improve. In U.K. Incidence is 7.2 cases / lac and in Japan incidence is 5.7 cases / lac. It accounts for over 2.5% cases of cancer in males and 2% of all cancers in females. In 11% cases more than one lesion of cancer is found in oesophagus.

**Predisposing factors-** These are- Achalasia, Collumnar lined lower oesophagus (Barrett's Oesophagus), Corrosive Lye Structure, Peterson Kelly Syndrome, Patient with tylosis, Smoking, Alcohol, Intake of nitrosamines as seen in bantu people. It is also important to be aware of the potential for further improvement that is offered by developments in oncology, laser and by evolving surgical techniques

**Epidemiology-** Mostly are squamous cell carcinoma. Adeno carcinoma is a different disease with a different etiology. It is due to malignant change in barretts oesophagus and is more common in western countries.

**Clinical history -** Any one above 40 years of age and complaints of painful swallowing or Dysphagia first to solids and then to semisolids and to liquids; should undergo appropriate diagnostic studies; Anemia; Respiratory infection

due to regurgitation overflow or fistualisation; Chest pain

**Clinical examination-**with examination of the neck to see for any lymphadenopathy

**Chest X-ray-**To see for nodes in mediastinum and any sign of aspiration or fistula formation; secondaries in lung and ribs etc.

**Barium swallow-** To see extent and site of obstruction; to see for change in the axis of oesophagus; any evidence of fistulisation

**Endoscopy -**To see the level of the disease; type of lesion, obstructive or ulcerative; to plan surgical resection accurately; synchronuos lesions; regular annual endoscopy and biopsy in case of barretts oesophagus; minimum of four quadrantric biopsies at 2cm intervals.

**Video endoscopy-**Modern endoscopy gives excellent views of the whole oesophagus and even small lesions can be clearly seen. Lesions with a modular or irregular surface tend to invade deeper than those with a granular or fine surface.

Thus lesions which are easily detectable by conventional endoscopic observation, have already been invaded into the submucosal layer or deeper. It is for this reason that oesophageal irrigation and iodine staining is widely used in Japan. All cancerous lesions at any depth of invasion remain stained with iodine. Not all unstained lesions are carcinoma.

**Ultra sound-** To see for lymphnodes metastasis in neck, chest, mediastinum,

celiac axis and secondaries in the liver.

**Endoscopic ultrasonography-**

This is used for staging for primary lesion and evaluating lymphnode spread. This is the best method. With high frequency probes normal oesophageal wall is seen as a five layer structure and sometimes seven layers of alternating hyperechoic and hypoechoic bands. E.U.S. (Endoscopic Ultrasound) Seems particularly useful for assessing very early cancer that may be amenable to mucosal resection or ablation. It could also have a place for the selection of the group of patients who might be entered into prospective randomized studies of preoperative treatment with drugs or radiation. The depth of tumor invasion can be assessed with 85% accuracy by E.U.S. Lymph node invasion can be detected with 87% accuracy, because smaller nodes can be seen and the internal architecture can be assessed

**Limitation of E.U.S-**Main limitation at present is that the instrument has a 4 cm Rigid Tip & is 13mm in diameter and it may not be possible to pass it through the tumor. Newer probes that can be passed down the biopsy channel of a standard endoscope have. However, been developed and are better for assessing surgical lesion than the deeply invading lesion that is likely to produce marked stenosis

**CT Scan & MRI-** CT Scan of chest, liver, lung and bone. Before embarking on a resection, CT of thorax is done to see for lymph node invasion. In a study from Osaka City University Hospital

3661 nodes were analysed which were removed in 72 patients who had extended lymphadenectomy. It showed that 8 mm diameter gave the best discrimination between invaded and noninvaded nodes with a sensitivity of 65% and specificity of 76%. CT & MRI can detect nodes of 1 cm diameter. Nodes detected on CT have 86% chance of being invaded. However, nodes below the tracheal bifurcation may be larger yet still not invaded.

**MRI-** It may be better than CT for detecting tracheo bronchial invasion if the criterion for a positive examination includes disappearance of a high intensity signal between the oesophageal wall, the trachea or bronchus. This strong signal is thought to be generated by the normal tracheo bronchial membrane.

**Patient assessment-** Once the diagnosis is made all patients of oesophageal cancer should be assessed as candidates for curative treatment. The aim of this assessment is to offer potentially curative treatment to those in whom there is a reasonable expectation of cure; to avoid inappropriately aggressive treatment in those who are not likely to be cured. Presence of metastatic disease detected by any method of imaging should be confirmed by biopsy if at all possible. None of the imaging method is 100% reliable and it is a tragedy to refuse potentially curative treatment to a patient, because of over interpretation of CT scan or ultrasound. Lymphnodes are detected as oval hypoechoic areas. Nodes as small as 3 mm can be detected; the diagnosis of metastasis is based on diameter of the node and the ratio of the smaller : larger diameter >0.5 indicates invasion; Characteristics of the border and the internal echo of the node are also helpful. Nodes with a clear border and uneven coarse, scattered, internal echo can be

diagnosed as metastatic with an accuracy of 87%.

**Surgical treatment-** Surgical excision of oesophagus for the treatment of cancer has improved considerably in recent years because of developments in Anesthetic management; Surgical Technique; Preoperative care; Pain relief. It is accepted that reasonable results can be achieved with surgical excision provided that careful attention is paid to case selection and to the details of operative techniques. Good nutritional advice and the sensible use of dietary supplements and substitutes, particularly liquid diet is an important aspect of the treatment.

**Surgery radical excision-** It involves removal of primary tumor and other tissues that might be invaded. Tumors in oesophagus have a propensity for extensive proximal spread in the submucosal lymphatics and hence surgical clearance should take account of this and generous proximal clearance is commonly recommended.

**General support-** Oesophageal cancer, and the process of assessment and treatment are extremely stressful to the patient and their relatives even when cure is achieved hence considerable effort needs to be directed to general care, to counselling and to psychological support.

### **Surgery**

**Iver Lewis Or Lewis Tanner procedure-** Most widely practiced procedure. This is the most straight forward and versatile method of access. Anastomosis may be done at thoracic inlet or in neck.

**Transhiatal oesophagectomy-** Without thoracotomy has enjoyed considerable popularity. It is more difficult to perform truly radical

resection. Complete lymphadenectomy is impossible by transhiatal surgery. It should be reserved for those who are unfit for radical surgery or for when palliation is all that can be achieved. Salama and leong (Nottingham) reported overall 5 years survival of 36% for squamous cell carcinoma but only 3% for adeno CA. This shows that cancer oesophagus is a bad disease but it is not untreatable. Survival as with all cancers is stage related and overall survival figures reflect the stage mix within individual series.

**Mckeowen** popularised the concept of subtotal oesophagectomy in U.K. In this operation only a small proximal stump is left behind and proximal tumour clearance is invariably complete for lesions as high as middle third. This was popularized by Mckeowen in the 1970s and was associated with 5 years survival of approximately 30% at a time when the average was 10-15%. Oesophago gastric anastomosis is above the level of the aortic arch.

**Three field node dissection-** Radical resection with methodical clearance of regional lymphnodes and adjacent tissues. The ultimate lymphnode clearance involves radical dissection in the abdomen chest and neck (3 fold dissection). This is widely practised in Japan with a low postop mortality. Rationale for this procedure was the relatively unsatisfactory outcome of conventional oesophagectomy with lymphnode dissection in the middle and lower mediastinum. Japanese indicated 5 years survival of 13.8%. Presently in some centres, if some cure seems possible, but there are significant operative risk factors 3 field node dissection is done in 2 stages. Oesophagectomy & mediastinal dissection is done first followed by cervico abdominal dissection and reconstruction three weeks later. In this

procedure, the nodes are dissected in the following tissue zone i.e. internal jugular vein, supraclavicular, recurrent laryngeal nerve, paratracheal, tracheal, bifurcation and pulmonary hilum, paraoesophageal, paraaortic, pulmonary ligament, superior & inferior diaphragmatic, perigastric (Pericardial) lesser curvature of stomach, left gastric, common hepatic and coeliac axis. The upper mediastinal nodes are dissected via a right thoractomy and the recurrent laryngeal nerves are taped the dissection is carried up through the thoracic inlet as far as possible. A collar incision is made in the neck and the dissection is carried out to the level of omohyoid muscle superiorly and external jugular vein laterally. This denudes the trachea, Bronchi and the right bronchial artery is preserved as far as possible to maintain tracheo bronchial circulation

**Complications**-After 3 field node dissection pulmonary complications occur in 16% cases. The dissection denerves the mediastinal trachea and main stem bronchi. Because of this there is impairment of cough reflex. Hence it is the practice to perform fibre-optic bronchoscopy once or twice a day for first 5 post op days. 30% patients developed recurrent laryngeal N Dysfunction. Part of this was responsible for significant incidence of regurgitation and pneumonia late in the recovery process.

**Minimally invasive surgery**-That is completely endoscopic resection of the oesophagus including gastric mobilization and anastomosis has been performed but it is an extraordinarily prolonged procedure and is at present impractical for routine use. Some groups have resected the oesophagus by Thoracoscope while the stomach has been mobilized at laparotomy. The

anastomosis has most cordially been performed in the neck. But intrathoracic stapled anastomosis has also been performed. Avoiding formal thoractomy seems rational but as yet surgical morbidity has not been reduced by endoscopic surgery and the procedure remains experimental. For the moment technique are still evolving and surgeons are improving their skills. If a useful method is developed it is vital that minimal access oesophagectomy is submitted for formal prospective randomized study.

In Osaka 138 patients underwent this procedure between 1980 - 1993. Hospital mortality was 5%. 5 years survival was 42% (100% for T1 Lesion and 34% in T4 lesion). Survival seemed more dependent on lymphnode invasion. More important groups are paraoesophageal, perigastric and rec. laryngeal nerve group lymphnodes.

Japanese results are better in the whole world because of the reasons such as-Less pressure on the operating theatre time in Japan. Allowing more time to be taken to do job thoroughly well; Patients stay in hospital much longer (mean duration including chemotherapy - 11 weeks post operative); Well trained assistants; Better interaction between surgeon, radiotherapist and chemotherapist; Good surgical techniques; Only done in hospital with adequate facilities; Resection is done in centre where at least one oesophageal resection is done every month.

British authors feel that resection should not be done if there is no chance of cure or only minimal chance while Japanese surgeons have a strong feeling that resection produces the best palliation but all agree that the concept of curative surgery is an important one and that the

primary aim of surgical resection should be cure whenever possible.

**Lesions of cardia** can be dealt with sub total oesophageal resection. Resection provided that the tumor in the proximal stomach can be cleared adequately and still leave enough stomach for a satisfactory reconstruction. Deemster has suggested subtotal oesophagectomy and total gastrectomy with reconstruction by colonic interposition in fit patients with potentially curable disease. This is a very major undertaking and only suitable for very carefully selected cases. Mortality of oesophageal resection is related to-Age ; Tumor size; Lung function (FEV1); Nutritional status and nutritional support. Radical treatment for oesophageal cancer is hazardous and it is therefore particularly important to assess the fitness of patients for any treatment that is proposed.

**Nutritional status and nutritional support**-Severe malnutrition indicates advanced cancer. If it occurs there is no point in attempting restoration to normal nutritional status before resection as this takes too long to be practical. Partial nutritional restoration has not shown to reduce the risk of oesophageal resection.

**Mortality following surgical resection has been significantly reduced**

- Methods of palliation have improved
- Chemotherapy has a much more predictable response rate
- This is not a disease that is untreatable a great deal can be done.
- Achieving the best results requires an experienced multidisciplinary team.



Adeno carcinoma of oesophagus is a more aggressive disease than squamous cell carcinoma

### Other methods of treatment

**Chemotherapy**-This has improved in recent years but is still not curative on its own. Preoperative chemotherapy with F.L.E.P. followed by concurrent chemoradiotherapy is active against locally advanced oesophageal cancer. In this series the pathologic complete response rate was 33% amongst those patients who underwent surgery. Before surgery 90 patients who had L.A.E.C. received chemotherapy i.e. 3 course of 5 FU. Leucovorin etoposide and cisplatin i.e. F.L.E.P. followed by concurrent chemoradiotherapy i.e. one course of cisplatin and etoposide combined with 4000 R. 4 weeks after radiation trans thoracic oesophagectomy was done

**Radiotherapy** -Survey of literature suggests that better cure rates are obtained by resection than by irradiation provided that operative mortality is low. Radiotherapy is presently the treatment of choice for cancer of the cervical oesophagus, it preserves voice and laryngeal function. In theory combination of surgery and radiotherapy should improve cure rate because each has different limitations in treating the primary lesion.

**Preoperative radiotherapy**-In eight randomized studies has shown benefit from combined treatment

**Post operative radiotherapy**-Has not been shown to have any benefit, but trials are few and lack statistical power. Non randomized studies have suggested a deleterious effect.

**Combined surgery and radiotherapy**-The outcome appears to

be better than those associated with surgery alone approximately doubling the 3 years survival. Patients with chemoradiotherapy had longer disease free survival but there were higher post operative complications. But given the failure of combined therapy to prolong overall survival we clearly need more effective less toxic regimes.

**Palliation**-Prevailing feeling is that if radical treatment is unlikely to achieve a cure, it is better to have swallowing restored in the least traumatic manner so that, if survival is short the remaining time is not spent in recovering from a big operation. The decision to pursue a palliative course of action is therefore taken in a greater proportion of cases and the technology of palliation is a subject of much interest. The methods available for palliation are- Dilation, Intubation, Laser, Bipolar diathermy, Alcohol injection, Endoluminal radiotherapy or brachy therapy, Expanding stents, Surgical palliation

**Dilatation** -Simple and relatively safe but gives only very temporary relief. Can be useful for tiding a patient over a period of assessment but is much less popular for palliation now.

**Intubation**-Endoluminal tubes to restore swallowing have been used for generations, but in the last 20 years tube design and methods of insertion have improved sufficiently to make techniques reasonably effective and safe. Tubes which need to be inserted during surgery are-Mouseau barbin and Celestin tube. The tubes inserted endoscopically commonly used is Atkinson tube. It is used most widely. It is relatively soft, funnel shaped and it gives reasonable palliation. But most patients are restricted to semi solid food only and there is significant perforation

rate (5-10%). Now are used self expanding endoluminal stents

**LASER**-Laser canalization is now widely used and many would consider this as the current method of choice. Good palliation is obtained with little morbidity and comparative trials have shown it to have small but significant advantage over intubation

**Disadvantages**-Procedure needs to be repeated regularly. Equipment is expensive and requires maintenance & is not portable. Considerable investment and time is required as lasers are expensive. Access to the lesion is not always ideal.

**Procedure** -Laser used is Nd Yag (Yttrium Aluminium Garnet). 90-100 watt laser used for 2 sec at 1 cm distance from the tissue beams aimed at neoplastic tumor closest to the tumor and treatment progresses to an increasing larger concentric circles towards but not to the wall of the oesophagus. If not completed in one sitting treatment can be carried out on subsequent sittings almost every other day. At the beginning of each laser after the first one the previously treated neoplastic tissue that plugs the lumen must be removed so that progressive coring out of the tumor can be done. Indicated in patients who have been rejected as surgical candidate even for palliation due to location or local spread of tumor or due to patients clinical status.

**Advantages of LASER**- It averts the need for surgery. It diminishes considerably likelihood of systematic side effect. Can be performed under direct vision. Unlike radiotherapy, there is no maximum dose and so if tumor recurs in same area re-treatment can be given

**Advancement in LASER use-**

With the marriage of computer and laser technology. The selection of proper dose for a given problem will be refined. Use of tissue sensitized agents to allow for more precise destruction of neoplastic tissue with less damage to normal tissue. Progress in the development of endoscopes and endoscopic accessories will render the target lesion better accessible to laser treatment.

**Results & risks**-In one series it gave symptomatic improvement in 37 out of 40 cases Endoscopic luminal diameter is improved from nil to 11.5mm. There is risk of perforation and T.O.Fistula

**Bipolar diathermy**-Bipolar tumor probe diathermy has shown to produce similar results to laser with circumferential tumor. The equipment is much less expensive than laser. But it is not applicable to polypoidal tumors that do not encircle the oesophagus. A probe with a 180 degree contract plate is available for polypoid lesions. But it is difficult to use in practice.

**Alcohol injection**-Endoscopic tumor necrosis with 100% ethanol is simple and cheap and may have results similar to laser and diathermy. A simple endoscopic injection needle is used to inject small aliquots of alcohol in the tumor throughout its length. Relief of dysphagia may take a few days but good quality palliation can be produced. The period of 48 hours between treatment generally allows for maximal tissue necrosis and is well tolerated by patients

**Endo luminal radiotherapy or brachy therapy (E.R.)**-E.R. with a source that produces little tissue penetration (Brachy Therapy) is simple and effective method of palliation with a low complication rate. In common with laser the equipment is expensive but relief

of dysphagia can be prolonged.

**Expanding stents** -These are the latest addition to the armamentarium. These are expensive but have the advantage of producing excellent relief of dysphagia with a single procedure Cumulative hospital costs are lower as repeated treatments are not required. No serious complication. Prospective trials are going to decide, which of the available designs is best. Commonly used are ultraflex and Z stents.

**Surgical palliation**-Palliative resection gives excellent relief of dysphagia but it is a major procedure with significant disadvantages, specially when expected survival is short. When cure is not possible, surgical resection should be discouraged

**Endoscopic mucosal resection**-If lesion invades submucosa incidence of lymphnode metastasis is 40-60%.Lymphnode permeation is 70-80%. If lesion is confined to mucosa the incidence of lymphnode metastasis is 4-7%. If lesion is epithelial, no metastasis occurs. Hence in recent years enthusiasm has gone for the technique of endoscopic mucosal resection in very early cases i.e. epithelial or mucosal specially in elderly or unfit patients. E.M.R. Involves raising the lesion by submucosal injection of saline and diathermy excision of the affected portion.

At present E.M. is recommended

- if there are 5 or fewer lesions
- the lesion is smaller than 6 cm
- it does not occupy the whole circumference of the oesophagus

### Conclusion

- Treating cancer of the oesophagus remains a challenge

- Prevailing attitude is one of despair and results fall short of what one would like to achieve.
- Considerable progress has however, been made in last three decades.
- If, diagnosis is made at an earlier stage then complications such as oesophago bronchial fistula are less common
- In carcinoma of oesophagus laparoscopy have resulted in acceptable resection and survival rate. Endoscopic ultrasound helps to evaluate the extent of oesophageal wall involvement. Survival for this disease is still largely stage dependant and earlier diagnosis probably holds the key to improved diagnosis.

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Approximately 70% to 80% of patients with newly diagnosed bladder cancer will present with superficial bladder tumors (i.e., stage Ta, Tis, or T1). Those who do present with superficial, noninvasive bladder cancer can often be cured, and those with deeply invasive disease can sometimes be cured by surgery, radiation therapy, or a combination of modalities that include chemotherapy.<sup>1</sup> Studies have demonstrated that some patients with distant metastases have achieved long-term complete response following treatment with combination chemotherapy regimens.

### Prognostic factors

The major prognostic factors in carcinoma of the bladder are the depth of invasion into the bladder wall and the degree of differentiation of the tumor. Most superficial tumors are well differentiated. Patients in whom superficial tumors are less differentiated, large, multiple, or associated with carcinoma in situ (Tis) in other areas of the bladder mucosa are at greatest risk for recurrence and the development of invasive cancer. Such patients may be considered to have the entire urothelial surface at risk for the development of cancer. Tis may exist for variable durations. Adverse prognostic features associated with a greater risk of disease progression include the presence of multiple aneuploid cell lines, nuclear p53 overexpression, and expression of the Lewis-x blood group antigen.<sup>2,5</sup> Patients with Tis who have a complete

response to bacillus Calmette-Guérin have approximately a 20% risk of disease progression at 5 years; patients with incomplete response have approximately a 95% risk of disease progression.<sup>2</sup> Several treatment methods (i.e., transurethral surgery, intravesical medications, and cystectomy) have been used in the management of patients with superficial tumors, and each method can be associated with 5-year survival in 55% to 80% of patients treated.<sup>2,3,6</sup>

Invasive tumors that are confined to the bladder muscle on pathologic staging after radical cystectomy are associated with approximately a 75% 5-year progression-free survival rate. Patients with more deeply invasive tumors, which are also usually less well differentiated, and those with lymphovascular invasion experience 5-year survival rates of 30% to 50% following radical cystectomy.<sup>7</sup> When the patient presents with locally extensive tumor that invades pelvic viscera or with metastases to lymph nodes or distant sites, 5-year survival is uncommon, but considerable symptomatic palliation can still be achieved.<sup>8</sup>

Expression of the tumor suppressor gene p53 also has been associated with an adverse prognosis for patients with invasive bladder cancer. A retrospective study of 243 patients treated by radical cystectomy found that the presence of nuclear p53 was an independent predictor for recurrence among patients with stage T1, T2, or T3 tumors.<sup>9</sup> Another retrospective study showed p53

expression to be of prognostic value when considered with stage or labeling index.<sup>10</sup>

### Tumour staging

The clinical staging of carcinoma of the bladder is determined by the depth of invasion of the bladder wall by the tumor. This determination requires a cystoscopic examination that includes a biopsy, and examination under anesthesia to assess the size and mobility of palpable masses, the degree of induration of the bladder wall, and the presence of extravesical extension or invasion of adjacent organs. Clinical staging, even when computed tomographic and/or magnetic resonance imaging scans and other imaging modalities are used, often underestimates the extent of tumor, particularly in cancers that are less differentiated and more deeply invasive.<sup>11</sup>

The American Joint Committee on Cancer (AJCC) has designated staging by TNM classification to define bladder cancer.<sup>12</sup>

### Primary tumor (T)

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Ta: Noninvasive papillary carcinoma
- Tis: Carcinoma in situ (i.e., flat tumor)
- T1: Tumor invades subepithelial connective tissue

- T2: Tumor invades muscle
- pT2a: Tumor invades superficial muscle (inner half)
- pT2b: Tumor invades deep muscle (outer half)
- T3: Tumor invades perivesical tissue
- pT3a: Microscopically
- pT3b: Macroscopically (extravesical mass)
- T4: Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, or abdominal wall
- T4a: Tumor invades the prostate, uterus, vagina
- T4b: Tumor invades the pelvic wall, abdominal wall

[Note: The suffix “m” should be added to the appropriate T category to indicate multiple lesions. The suffix “is” may be added to any T to indicate the presence of associated carcinoma in situ.]

### Regional lymph nodes (N)

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Metastasis in a single lymph node, = 2 cm in greatest dimension
- N2: Metastasis in a single lymph node, > 2 cm but = 5 cm in greatest dimension; or multiple lymph nodes, = 5 cm in greatest dimension
- N3: Metastasis in a lymph node, > 5 cm in greatest dimension

### Distant metastasis (M)

- MX: Distant metastasis cannot be assessed

- M0: No distant metastasis
- M1: Distant metastasis

### AJCC stage groupings

Stage 0a : Ta, N0, M0

Stage 0is : Tis, N0, M0

Stage I: T1, N0, M0

Stage II: T2a, N0, M0, T2b, N0, M0

Stage III: T3a, N0, M0, T3b, N0, M0, T4a, N0, M0

Stage IV: T4b, N0, Any T, N1/N2/N3 M0

### Treatment option overview

Prolonged survival in most patients with superficial cancers is achieved by transurethral resection (TUR) with or without intravesical chemotherapy. Cure is not possible for the majority of patients with deeply invasive tumors and for most patients with regional or distant metastases. In North America, the standard treatment of patients with invasive bladder cancers is radical cystectomy and urinary diversion. Other treatment approaches include TUR and segmental resection with or without radiation therapy, combined chemotherapy-radiation therapy, or either followed by salvage cystectomy, when needed, for local failure.<sup>13,14</sup> Reconstructive techniques that fashion low-pressure storage reservoirs from the reconfigured small and large bowel eliminate the need for external drainage devices and, in some male patients, allow voiding per urethra. These techniques are designed to improve the quality of life for patients who require cystectomy.<sup>15</sup>

### Stage- 0 bladder cancer

Patients with stage 0 bladder tumors can be cured by a variety of treatments, even though the tendency for new tumor

formation is high. Patients at greatest risk of recurrent disease are those whose tumors are large, poorly differentiated, multiple, or associated with nuclear p53 overexpression. In addition, patients with carcinoma in situ (Tis) or dysplasia of grossly uninvolved bladder epithelium are at greater risk of recurrence and progression. Transurethral resection (TUR) and fulguration are the most common and conservative forms of management. Careful surveillance of subsequent bladder tumor progression is important. Patients who require more aggressive forms of treatment are those with extensive multifocal recurrent disease and/or other unfavorable prognostic features. Segmental cystectomy is applicable to only a small minority of patients because of the tendency of bladder carcinoma to involve multiple regions of the bladder mucosa and to occur in areas that cannot be segmentally resected.

Intravesical therapy with thiotepa, mitomycin, doxorubicin, or bacillus Calmette-Guérin (BCG) is most often used in patients with multiple tumors or recurrent tumors or as a prophylactic measure in high-risk patients after TUR. Administration of intravesical BCG plus subcutaneous BCG following TUR was compared with TUR alone in patients with Ta and T1 lesions. Treatment with BCG delayed progression to muscle-invasive and/or metastatic disease, improved bladder preservation, and decreased the risk of death from bladder cancer. Two nonconsecutive 6-week treatment courses with BCG may be necessary to obtain optimal response.<sup>16</sup> Patients with a T1 tumor at the 3-month evaluation after a 6-week course of BCG and patients with Tis that persists after a second 6-week BCG course have a high likelihood

of developing muscle-invasive disease and should be considered for cystectomy.<sup>17</sup> Although BCG may not prolong overall survival for Tis disease, it appears to afford complete response rates of about 70%, thereby decreasing the need for salvage cystectomy

### Standard treatment options

- TUR with fulguration.<sup>17</sup>
- TUR with fulguration followed by intravesical BCG. BCG is the treatment of choice for Tis.<sup>5,7,9,13,14</sup>
- TUR with fulguration followed by intravesical chemotherapy.<sup>2,11,17</sup>
- Radical cystectomy in selected patients with extensive or refractory superficial tumor.<sup>17,18</sup>

### Stage- I bladder cancer

Patients with stage I bladder tumors can be cured by a variety of treatments, even though the tendency for new tumor formation is high. In a series of patients with Ta or T1 tumors who were followed for a minimum of 20 years or until death, the risk of bladder recurrence following initial resection was 80%.<sup>18</sup> Patients at greatest risk of recurrent disease are those whose tumors are large, poorly differentiated, multiple, or associated with dysplasia of grossly uninvolved bladder epithelium. Transurethral resection (TUR) and fulguration are the most common and conservative forms of management. Careful surveillance of subsequent bladder tumor progression is important. Patients who require more aggressive forms of treatment are those with extensive multifocal recurrent disease and/or other unfavorable prognostic features. Segmental cystectomy is applicable to only a small minority of patients because of the tendency of

bladder carcinoma to involve multiple regions of the bladder mucosa and to occur in areas that cannot be segmentally resected.

Intravesical therapy with thiotepa, mitomycin, doxorubicin, or bacillus Calmette Guérin (BCG) is most often used in patients with multiple tumors or recurrent tumors or as a prophylactic measure in high-risk patients after TUR.

### Standard treatment options

- TUR with fulguration.<sup>19</sup>
- TUR with fulguration followed by intravesical BCG.<sup>20</sup>
- TUR with fulguration followed by intravesical chemotherapy.<sup>20</sup>
- Radical cystectomy in selected patients with extensive or refractory superficial tumor
- Interstitial implantation of radioisotopes with or without external-beam radiation therapy

### Stage- II bladder cancer

Stage II bladder cancer may be controlled in some patients by transurethral resection (TUR), but often more aggressive forms of treatment are dictated by recurrent tumor or by the large size, multiple foci, or undifferentiated grade of the neoplasm. Segmental cystectomy is appropriate only in very selected patients. Radical cystectomy is considered standard treatment.

After radical cystectomy, however, an approximate 50% risk of recurrence still exists for patients with muscle-invasive disease. The addition of preoperative radiation therapy to radical cystectomy does not result in any survival advantage when compared with radical cystectomy alone. Since the disease commonly recurs with distant metastases, systemic

chemotherapy administered before or after cystectomy has been evaluated as a means of improving outcome. Administration of chemotherapy before cystectomy (i.e., neoadjuvant) may be preferable to postoperative treatment because tumor downstaging from chemotherapy may enhance resectability, occult metastatic disease may be treated as early as possible, and chemotherapy may be better tolerated. A meta-analysis of 10 randomized trials of neoadjuvant chemotherapy, including updated data for 2,688 individual patients, showed that platinum-based combination chemotherapy was associated with a significant 13% relative reduction in the risk of death and resulted in an improvement in 5-year survival from 45% to 50% ( $P = .016$ ). Neoadjuvant single-agent cisplatin was not associated with any such survival benefit in the meta-analysis.<sup>21</sup> Based on these findings, it is reasonable to offer neoadjuvant platinum-based combination chemotherapy prior to cystectomy in patients with muscle-invasive bladder cancer.

In patients who are not willing or able to undergo radical cystectomy, definitive radiation therapy is an option that yields a 5-year survival of approximately 30%.<sup>22</sup> Approximately 50% of patients have dysuria and urinary frequency during treatment, which resolves several weeks after treatment, and 15% report acute toxic effects of the bowel.

Systemic chemotherapy has been incorporated with definitive radiation therapy to develop a more effective bladder-sparing approach for patients with locally advanced disease. The utility of this multimodality approach was confirmed in a prospective, randomized comparison of radiation therapy and chemoradiation therapy,

which reported an improved rate of local control when cisplatin was given in conjunction with radiation therapy, even though there was no improvement in the rate of distant metastases or overall survival.<sup>23</sup> In a phase III study, the Radiation Therapy Oncology Group evaluated the potential benefit of adding 2 cycles of neoadjuvant methotrexate, cisplatin, and vinblastine prior to concurrent cisplatin and radiation therapy, but neoadjuvant chemotherapy was associated with increased hematologic toxic effects and yielded no improvement in response rate, freedom from distant metastases, or overall survival when compared with chemoradiation therapy alone.<sup>24</sup> Because no randomized trials have directly compared the bladder-preserving chemoradiation therapy approach with radical cystectomy, it is not clear if the former is as effective as the latter. Choice of treatment should be guided by a patient's overall medical condition and by consideration of the adverse effects of therapy.

### Treatment options

- Radical cystectomy with or without pelvic lymph node dissection
- Neoadjuvant platinum-based combination chemotherapy followed by radical cystectomy
- TURBT / External-beam radiation therapy / Chemotherapy alone in patients with multiple comorbidities and poor PS.
- TURBT followed by RT & concurrent Chemotherapy.
- Segmental cystectomy (solitary lesion).

### Stage- III bladder cancer

For most patients, radical cystectomy is

considered standard treatment. Radical cystectomy includes removal of the bladder, perivesical tissues, prostate, and seminal vesicles in men and the uterus, tubes, ovaries, anterior vaginal wall, and urethra in women and may or may not be accompanied by pelvic lymph node dissection

After radical cystectomy, however, an approximate 50% risk of recurrence still exists for patients with muscle-invasive disease. A meta-analysis of 10 randomized trials of neoadjuvant chemotherapy, including updated data for 2,688 individual patients, showed that platinum-based combination chemotherapy was associated with a significant 13% relative reduction in the risk of death and resulted in an improvement in 5-year survival from 45% to 50% ( $P = .016$ ). Neoadjuvant single-agent cisplatin was not associated with any such survival benefit in the meta-analysis.<sup>21</sup> Based on these findings, it is reasonable to offer neoadjuvant platinum-based combination chemotherapy prior to cystectomy in patients with muscle-invasive bladder cancer.

In patients who are not willing or able to undergo radical cystectomy, definitive radiation therapy is an option that yields a 5-year survival of approximately 30%. Randomized trials, conducted from the 1950s through the 1980s, of definitive radiation therapy (with salvage cystectomy only for incomplete response or failure) versus preoperative radiation therapy followed by cystectomy have found similar or worse survival in patients who received definitive radiation therapy.<sup>23</sup>

Systemic chemotherapy has been incorporated with definitive radiation therapy to develop a more effective

bladder-sparing approach for patients with locally advanced disease. The utility of this multimodality approach is same as mentioned above for stage II bladder cancer. In some nonrandomized studies, 50% or more of patients who had bladder-preserving therapy (i.e., initial transurethral resection of as much tumor as possible followed by concurrent chemoradiation therapy) were alive at 5 years, and 75% of those survivors had an intact bladder.<sup>24</sup> Because no randomized trials have directly compared the bladder-preserving chemoradiation therapy approach with radical cystectomy, it is not clear if the former is as effective as the latter. Choice of treatment should be guided by a patient's overall medical condition and by consideration of the adverse effects of therapy.

### Treatment options

- Radical cystectomy with or without pelvic lymph node dissection.
- Neoadjuvant platinum-based combination chemotherapy followed by radical cystectomy
- External-beam radiation therapy with or without concurrent chemotherapy. (Organ preservation / treatment for unfit patients)

### Stage- IV bladder cancer

Currently, only a small fraction of patients with stage IV bladder carcinoma can be cured. These patients may undergo radical cystectomy with pelvic lymph node dissection. The extent of lymph node dissection during cystectomy is controversial<sup>2</sup> as there are no data from prospective trials demonstrating improved outcomes with lymph node dissection. Definitive radiation therapy with or without concurrent chemotherapy, evaluated mainly in

patients with locally advanced (T2-T4) disease, appears to have minimal curative potential in patients with regional lymph node metastases.

The focus of care for many stage IV patients is on palliation of symptoms from bladder tumor that is often massive. Urinary diversion may be indicated, not only for palliation of urinary symptoms, but also for preservation of renal function in candidates for chemotherapy. Platinum-based combination chemotherapy regimens are the standard of care. Gemcitabine has shown activity in phase II trials of patients with metastatic bladder cancer.<sup>25</sup> In a multicenter, randomized, phase III trial comparing the combination of gemcitabine/cisplatin (GC) with the M-VAC regimen in 405 patients with advanced or metastatic bladder cancer, GC yielded similar response rates, time-to-progression, and overall survival (hazard ratio [HR] = 1.04; 95% confidence interval [CI], 0.82-1.32; *P* = .75) compared with M-VAC, but GC had a better safety profile and was better tolerated than M-VAC. Although this study was not designed to show the equivalence of the 2 regimens, the similar efficacy and reduced toxic effects of GC make it a reasonable alternative in patients who may not tolerate the M-VAC regimen.<sup>26</sup>

**For patients with T4b, N0, M0; Any T, N1, M0; Any T, N2, M0; Any T, N3, M0**

#### Treatment options

- Radical cystectomy with pelvic lymph node dissection.
- External-beam radiation therapy.
- Urinary diversion or cystectomy for palliation.

- Chemotherapy as an adjunct to local treatment.

**For patients with Any T, Any N, M1 disease**

#### Treatment options

- Chemotherapy alone or as an adjunct to local treatment.<sup>3,4,9</sup>
- External-beam radiation therapy for palliation.
- Urinary diversion or cystectomy for palliation.

#### Recurrent bladder cancer

The prognosis for any patient with progressive or recurrent invasive bladder cancer is generally poor. Management of recurrence depends on prior therapy, sites of recurrence, and individual patient considerations. Recurrent or progressive disease in distant sites or after definitive local therapy has an extremely poor prognosis, and clinical trials should be considered whenever possible.

In patients with recurrent transitional cell carcinoma, combination chemotherapy has produced good response rates with occasional complete responses seen.<sup>27</sup> Chemotherapy agents that have shown activity in metastatic bladder cancer include: paclitaxel, ifosfamide, and gemcitabine.<sup>28</sup>

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# Wound Healing

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## Review article

The term Healing refers to the replacement of destroyed tissue by living tissue. Healing Process has two aspects Contraction - A mechanical reduction in the size of the defect occurring in the first few weeks. Replacement of lost tissue- This is brought about by-Migration of cells and by division of adjacent cells to provide extra time to fill the gap. This is accomplished in two ways-Regeneration (Replacement of lost tissue by tissue similar in type due to the proliferation of surrounding undamaged specialized cells); Repair (The replacement of lost tissue by granulation tissue, which matures to form scar tissue. This is inevitable when the surrounding specialized cells do not possess the capacity to proliferate eg. Muscles and neurons).

Wound healing is a complicated process involving:

- Movement of cells
- Division of cells
- Rearrangement of tissues
- Bio-chemical changes.

In healing the phases are as follows:-

- **Lag phase** : No marked changes are seen in the wound for few days.
- **Rapid change in size due to contraction** : Bio-chemical changes are in the early period. On Microscopic examination there is an acute inflammatory reaction, in initial period and rapid cell division

is more conspicuous later.

### Basic things that happen in wound healing are

- Wound contraction
- Granulation tissue formation
- Bio-chemical changes

### Wound contraction

- **Lag phase** : Initially for 2-3 days followed by.
- **Period of rapid contraction** : Which is largely completed by 14<sup>th</sup> Day. Wound is reduced by approximately 80% of its original size Contraction of wound results in much faster healing as 1/4<sup>th</sup> to 1/3<sup>rd</sup> amount of new tissues have to be formed.

**Causes of wound contraction** : No definite causes are known. But accepted ones are-removal of fluid by drying; contraction of collagen (It is supposed that the contracting mechanism lies in the edge of the wound, the so called "picture frame area". Interference with this area delays contraction).

### Factors which inhibit wound contraction

- X-ray radiation or chemo-therapy.
- Corticosteroids
- Burns.
- Immediate skin grafting of the Raw wound prevents contraction.

### Granulation tissue formation

Three phases are observed in this process.

Damaged cells set in motion the phenomenon of Acute Inflammation

- An exudation of fibrin and polymorphs develop.
- Hemorrhage also occurs and the blood clot contributes to fibrin formation.
- Ground substance undergoes depolymerisation.
- Loss of granules happen in mast cells.

### Phase of demolition

- Dead tissue cells liberate their autolytic enzymes.
- Proteolytic enzymes come from disintegrating polymorphs.
- There is associated mononuclear infiltration with large phagocytic macrophages. These digest or remove particulate matter.
- Fusion of macrophages leads to formation of foreign body giant cells.

### In-growth of granulation tissue

It is formed by the proliferation and migration of the surrounding connective tissue elements. It is composed of, in the first instance, capillary loops and fibroblasts together with a variable number of inflammatory cells. It is thus a highly vascular tissue but with the passage of time it develops into a vascular scar tissue. There are two stages-Stage of vascularisation followed by stage of devascularisation

**Stage of vascularisation-** There is ingrowth of capillary loops and fibroblasts so that the insoluble fibrin clot is converted into living vascular granulation tissue and is known organization. Blood clot and inflammatory exudates is invaded by macrophages followed by capillary loops and fibroblasts. Formation of vascular arcades. Newly formed blood vessels leak proteins. Some of the newly formed blood vessels develop smooth muscle coat and form arterioles. Fibroblasts which accompany capillary loops are at first large and plump but gradually collagen fibres form around them and the cells become mature, elongated fibrocytes. Fibroblasts are responsible for the production of the mucopolysaccharide ground substance.

The nerve fibres and lymphatics are formed from the existing nerve fibres and lymphatics in the surrounding region.

**Stage of devascularisation-** As fibroplasia proceeds, some blood vessels undergo atrophy while others show endarteritis obliterans. Sometimes this phase is followed by cicatrization and leads to contraction.

### Factors affecting granulation tissue formation

**Scurvy** - Maturation of collagen does not occur in absence of vitamin C.

**Cortisone administration-** Decreases granulation tissue formation as seen in animals but in human beings the dose in which cortisone is given, does not influence wound healing.

**Protein starvation** - Lack of adequate proteins decrease wound healing

### Bio-chemical considerations -

a. **Early productive phase-** In this phase protein containing methionine

is accumulated. During this protein and hexosamine content is increased. This indicates that good ground substance is being formed.

b. **Collagen phase-** Cystine containing proteins also accumulate at this time and hexosamine level of wound gradually diminishes. As fibroplasia proceeds. Hydroxyproline content of wound increases.

**Tensile strength-** This is estimated by the force necessary to disrupt the wound. This is related to granulation tissue and collagen formation. It is affected by:-

**Direction of the wound-** Skin wounds made in the direction parallel to the lines of LANGER heal faster than those made perpendicular to them. The lines of LANGER are due to the orientation of collagen bundles in dermis. Skin incision made across the lines of LANGER tend to gape and their healing is delayed.

**Abdominal support** - Abdominal binders reduce the rate of gain of tensile strength.

**Effect of previous wounding** - Resutred wounds heal faster than those sutured primarily because the reparative process has already commenced.

**Severe trauma** - Delays wound healing due to the adrenal cortical response to stress.

### Complications of wound healing

- Infection
- Implantation of epidermoid cyst.
- Neoplasia (squamous cell carcinoma).
- Keloid formation.

- Pigmentary changes.
- Painful scar
- Weak scar
- Cicatrization

### Factors influencing wound healing

#### Local factors

- Poor blood supply - Delays wound healing
- Exposure to ionising radiations eg. X-ray - delay wound healing.
- Adhesions to bony surfaces - delays wound healing
- Infection
- Movement
- Neoplasia
- Trauma
- Ultra-violet rays helps in wound healing.

#### General factors

- **Age** - healing is faster in young individuals.
- **Nutrition** - In protein deficiency there is delay in wound healing.
- **Scurvy** - In Deficiency of Vitamin C there is presence of excessive amount of poorly sulphated ground substance and lack of maturation of collagen fibres.
- **Hormones**
- Corticosteroids delay wound healing in animals. In human being chronic long term use delays wound healing.
- Desoxy corticosterone acetate and anabolic steroids help in wound healing.
- **Temperature** : Wounds heal slowly in cold weather. Optimum temp in 30°C.

- **Oxygen** - Collagen synthesis is increased by raising the concentration of inspired oxygen.
- **Zinc** - it helps in bio-synthesis of collagen.
- **Metabolic disease** - like diabetes, jaundice and uremia delay wound healing.

**Wound healing** - Wound healing is the summation of number of processes which follow injury, including

- Coagulation
- Inflammation
- Matrix synthesis and deposition
- Angiogenesis
- Fibroplasia
- Epithelisation Contraction
- Remodeling
- Scar maturation

### Wound dehiscence

Suture failure plays an important role:

There is poor connective tissue formation in the scar. Causes are:-

- Local sepsis and intra abdominal collection of pus or fluid.
- Mass of implanted dead tissue.

For repair - Use non absorbable monofilament sutures. Wound dehiscence reflects an error of judgment on the part of the Surgeon i.e. failure to assess the risk of break - down and adopt the appropriate wound closure technique to prevent it.

- Avoid tying the sutures too tight; this compromises the perfusion of the wound.
- Interrupted sutures are more secure than continuous suture.

**Intra abdominal infection** - is the well known risk factor for wound

dehiscence.

- Overall 44% of the patients with abdominal wound dehiscence had intra abdominal infection and in these patients mortality rate was double.
- Surgical technique of closure is important.
- Type of closure, type of suture and suture bites being taken 1 cm apart and 1 cm deep in facia are important.
- It is well established that age, obesity, infection and technique of closure influence the incidence of midline wound complications.

Israelsson suggests that suture length to wound length ratio i.e. SL : WL is also important. If SL : WL ratio is less than 4, the likelihood of abdominal wall dehiscence increases.

### Newer concepts in wound healing

**Hyperbaric Oxygen** - Use of hyperbaric oxygen in wound healing of ischemic limbs.

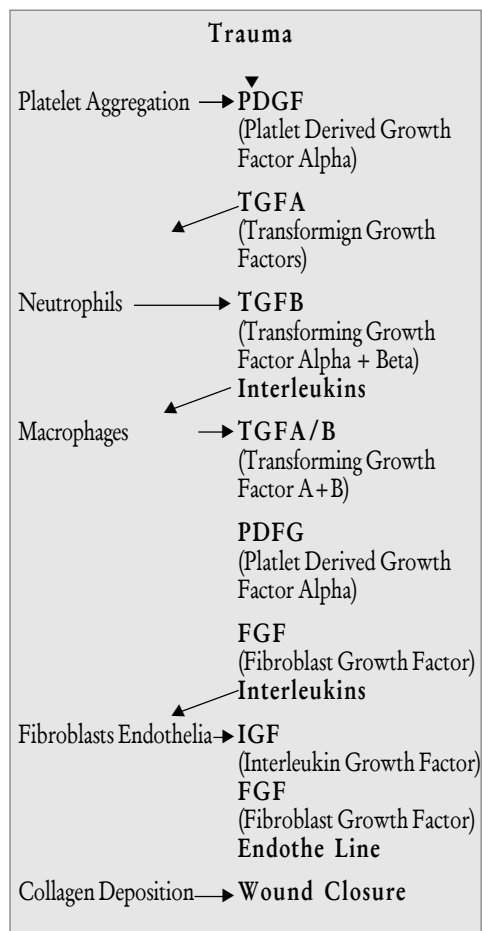
**Diabetes and wound healing** - Recent studies have demonstrated the importance of blood glucose control in the wound healing process and the role of insulin like growth factor in proper wound repair, due the deficient production of growth factors locally.

**Nitric oxide** - is an automatic regulator of wound fibroblast synthetic factor. Severe malnutrition and steroid use may diminish nitric oxide production by local inflammatory cells and decrease wound healing.

**Vacuum assisted closure** - Vacuum assisted closure or VAC technique produces good results in patients with chronic or otherwise difficult wounds. The application of sub-atmospheric

pressure eliminates chronic oedema, thus increasing localized blood flow. The force applied to the wound leads to enhanced formation of granulation tissue. The technique should be used to prepare the wound bed so that a lesser surgical procedure can be performed with a greater chance for successful wound closure, minimizing the time to complete wound closure and thus minimizing the cost, hospitalization and rehabilitation.

**Electrical stimulation of wound edges**- Stimulation with low dose current with implanted electrodes or surfaces electrodes has been shown to enhance wound healing in experimental cases.



Review  
article

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The management strategies for musculoskeletal tumours continue to evolve. Disease-free survival and functional outcome have improved with advances in diagnostic imaging, bioengineering, chemotherapy regimens, radiotherapeutic techniques, and surgical techniques including limb-sparing procedures<sup>1</sup>.

**History & clinical examination-** A detailed history followed by systematic clinical examination is essential to reach a clinical diagnosis and to plan the investigations and management.

**Investigations-** The following blood investigations and imaging studies help to reach a diagnosis, to consider the differential diagnoses and in the management of the tumour: Complete Blood Count, Prothrombin Time, Activated Partial Thromboplastin Time, Blood sugar, Serum Creatinine, Electrolytes, Uric acid, Liver Function Tests, Serum Calcium, Phosphorus and Parathormone, Good quality Radiographs of the involved part, Chest X-ray, Ultrasonogram of Abdomen, Bone Scintigraphy, CT scans with reconstruction images, CT scan of Chest, Magnetic Resonance Imaging, Angiogram, Positron Emission Tomography.<sup>2</sup>

**Biopsy-** Biopsy is the final step in the diagnostic pathway. The biopsy should provide sufficient tissue for gross pathological evaluation, histologic analysis, immunohistochemistry, and, if needed, electron microscopy and

cytogenetic testing. Biopsy incisions should be placed such that it will not compromise the definitive procedure. This is done by ensuring that the entire skin incision and biopsy track can be incorporated into the definitive surgical field and removed with the tumour, along with a cuff of normal tissue. Extremity incisions should be longitudinal to allow their incorporation at the time of definitive local surgery. The biopsy should avoid exposure and contamination of essential neurovascular structures and joints. Small, adequate incisions, meticulous haemostasis, and avoidance of creating skin or fascial flaps can help prevent local spread and contamination. If infection is considered, lesions should be cultured prior to giving prophylactic antibiotics. For most surgeons a well planned and executed open biopsy remains the gold standard, especially if there is no soft tissue component to the tumour, because it provides the best chance of obtaining representative tissue. Fine needle aspiration and core biopsy can be performed on most skeletal lesions. Image guidance like computerised tomography, ultrasound and fluoroscopy and specialised biopsy tools have led to an accuracy rate of 85% to 90%.<sup>3</sup> In future magnetic resonance imaging guided biopsies will enhance the accuracy of the procedure by focusing on the most viable section of the tumour. Biopsies done without proper planning, poorly placed incisions and complications of biopsy like non healing ulcers, sinus formation and tumour fungation can compromise

subsequent management of the tumour and lead to adverse prognosis.

**Staging of tumours-** Staging systems attempt to predict the prognosis and to evaluate the effect of therapeutic intervention by stratifying similar tumours according to various prognostic factors like the surgical grade, size, and compartmentalization of the tumour and the presence or absence of metastases<sup>2</sup>. Musculoskeletal neoplasms may be intracompartmental or extracompartmental. A compartment is defined as an anatomical space bounded by natural barriers namely bone, fascia, joint and muscle. Intracompartmental tumours are bounded in all dimensions by these natural barriers to extension of the tumour. Extracompartmental tumours are found in an extracompartmental location (eg: the popliteal space) or have extended beyond the natural barriers either by growth or by contamination from fracture, haemorrhage, or an operative procedure. Extracompartmental extension may be an indication of invasiveness<sup>3</sup>.

**Staging of benign tumours of bone** Enneking was the first to describe a system for the staging of benign musculoskeletal tumours, and this system is the one most commonly used (Table 1). The system is based on the biological behaviour of these tumours as suggested by radiographic findings. Benign tumours grow in a centrifugal fashion and a reactive capsule (in this case, bone) is formed as the response of the host to the tumour. The extent of the reactive

capsule reflects the rate at which the tumour is growing. Slowly growing tumours usually have a thick, well defined zone of transition, whereas those that are growing rapidly have a poorly defined or barely detectable zone. Because they lack histological uniformity, benign tumours of bone are graded on the basis of radiographic criteria. To distinguish them from the stages of malignant tumours, the stages of benign tumours are designated by Arabic numerals.

**Stage-1** tumours are classified as latent benign. Such tumours are usually asymptomatic and are commonly discovered as an incidental radiographic finding. Thick, dense reactive bone is present on both plain radiographs and CT scans. These lesions remain dormant and heal spontaneously in many instances. Examples include fibrous cortical defects, non-ossifying fibromas, and osteoid osteomas. Operative treatment usually is not necessary.

**Stage-2** indicates an active benign bone tumour. These tumours are actively growing and enlarging and therefore may be associated with physical signs and symptoms. In some instances, destruction of the cortex leads to a pathological fracture. A stage-2 tumour has a thin rim of reactive bone but remains intracompartmental. Examples include slowly expanding aneurysmal bone cysts and chondroblastomas. Operative curettage and bonegrafting are commonly used procedures for such tumours.

**Stage-3** benign bone tumour has little associated reactive bone and often breaks through the bone cortex. These lesions are likely to be growing faster than are Stage-1 or 2 lesions, and they are found both clinically and radiographically to be more locally invasive.

**Table- 1, Enneking Staging System for Primary Benign Tumours of Bone <sup>2</sup>**

Stage	Definition	Behaviour
1	Latent	Remains static or heals spontaneously
2	Active	Progressive growth but limited by natural barriers
3	Locally invasive	Progressive growth, not limited by natural barrier

Campanacci et al.<sup>4</sup> described a grading system for giant-cell tumours of bone that is based solely on radiographic appearance. A Grade-I tumour is well demarcated by a thin rim of reactive bone, with an intact or slightly thickened cortex without deformation.

Grade-II giant-cell tumours have relatively well defined margins but no radiopaque rim. The cortex is thin and expanded but intact.

Grade-II lesions associated with a fracture are considered separately.

Grade-III lesions demonstrate permeative growth in bone, with destruction of bone cortex and an associated soft-tissue mass.

**Staging of malignant tumours of bone**

The initial staging system for bone sarcomas was described by Enneking et al and adopted by the Musculoskeletal Tumour Society<sup>2,5,6</sup>. A surgical staging system for musculoskeletal sarcomas is accomplished by assessment of the surgical grade (G), the local extent (T), and the presence or absence of regional or distant metastases (M). The sarcomas for which this system was designed are those arising from the mesenchymal connective tissue of the musculoskeletal system. Lesions derived from the marrow, reticuloendothelial tissue housed within bone and mesenchymal soft tissue, and the skull are not included in this system because their natural

history, surgical management, and response to treatment are quite different. Thus leukemias, plasmacytomas, lymphomas, Ewing's sarcoma, undifferentiated round-cell lesions, and metastatic carcinomas are excluded

**Table -2, Enneking Staging System for Primary Malignant Tumours of Bone <sup>5, 6</sup>**

Stage	Tumour	Metastases	Grade
IA	T1	M0	G1
IB	T2	M0	G1
IIA	T1	M0	G2
IIB	T2	M0	G2
III	T1 or T2	M1	G1 or G2

Note—T1 = tumour is intracompartmental, T2 = tumour is extracompartmental, M0 = no regional or distant metastasis, M1 = regional or distant metastasis, G1 = low grade, G2 = high grade.

The American Joint Committee on Cancer devised a staging system which was recently revised<sup>7</sup>, and for cases diagnosed beginning January 1, 2003, the extent (T) of the tumour now reflects the size of the tumour rather than its transcortical extension. Tumours 8 cm or less in the greatest dimension are designated T1, whereas those greater than 8 cm are designated T2. Patients with small tumours generally have a better prognosis than those with large tumours.

A new designation, T3, has been added to indicate skip metastases—that appear to convey a better prognosis than osseous or hepatic metastases. This new AJCC staging system is summarized in Table 3. Note that there is now a defined stage III, representing a tumour without regional nodal (N0) or distant (M0) metastases, but with a skip metastasis (T3) in the affected bone. For high-grade tumours such as osteosarcoma, a skip lesion suggests a poor prognosis. This AJCC staging system does not apply to primary malignant lymphoma of bone or multiple myeloma, but is used for all other primary malignant tumours of bone (e.g., osteosarcoma, Ewing's sarcoma).

**Table-3, American Joint Committee on Cancer Staging System for Primary Malignant Tumours of Bone for those Tumours Diagnosed on or after January 1, 2003<sup>5, 7</sup>**

Stage	Tumour	Lymph Node	Metastases	Grade
IA	T1	N0	M0	G1 or G2
IB	T2	N0	M0	G1 or G2
IIA	T1	N0	M0	G3 or G4
IIB	T2	N0	M0	G3 or G4
III	T3	N0	M0	Any G
IVA	Any T	N0	M1a	Any G
IVB	Any T	N1	Any M	Any G
IVB	Any T	Any N	M1b	Any G

Note—Tx = primary tumour cannot be assessed, T0 = no evidence of primary tumour, T1 = tumour 8 cm or less in greatest dimension; T2 = tumour more than 8 cm in greatest dimension, T3 = discontinuous tumours in the primary bone; Nx = regional lymph nodes not assessed, N0 = no regional lymph node metastases, N1 = regional lymph node

metastasis; Mx = distant metastasis cannot be assessed, M0 = no distant metastasis, M1 = distant metastasis, M1a = lung, M1b = other distant sites; and Gx = grade cannot be assessed, G1 = well differentiated (low grade), G2 = moderately differentiated (low grade), G3 = poorly differentiated (high grade), G4 = undifferentiated (high grade).

**Operative margins according to Enneking<sup>2, 6</sup>**

Four types of margins based on the relationship of the surgical margin to the neoplasm and its pseudocapsular-reactive zone are recognised.

**Table- 4, Surgical Margins**

Type	Plane of dissection	Result
Intralesional macroscopic disease	Piecemeal debulking or curettage	Leaves disease
Marginal either "satellite"	Shell out <i>en bloc</i> through pseudocapsule or reactive zone	May leave/ "skip" lesions
Wide lesions	Intracompartmental <i>en bloc</i> with cuff of normal tissue	May leave
Radical	Extracompartmental <i>en bloc</i> entire compartment	No residual lesion

**Operative procedures- general recommendations**

An intralesional procedure (curettage) is performed for benign bone tumours of all stages. However, for many stage-2 and all stage-3 benign bone tumours, the margins of excision within the lesion are extended by power curettage and adjuvants such as phenol, methylmethacrylate, or liquid nitrogen. Still, it must be assumed that microscopic disease is left behind<sup>2</sup>.

**Table- 5, Operative procedures according to the system of Enneking et al<sup>6</sup>**

Margin	Local	Amputation
Intralesional amputation	Incisional biopsy	Debulking
Marginal amputation	Curettage or Debulking excision	Marginal
Wide amputation	Marginal excision	Wide
Radical amputation	Excisional biopsy	Radical
	Wide excision (intracompartmental)	Wide (through bone)
	Radical resection (extracompartmental)	Radical (through joint)

Excision through the perilesional reactive zone is indicated for recurrent stage-2 or stage-3 benign bone tumours, and possibly for some primary stage-3 tumours. Also, such excisions are used with success in patients who have a high or low-grade bone or sarcoma that has shown histological evidence of extensive necrosis in response to preoperative chemotherapy and radiation therapy. However, a higher prevalence of local recurrence can be expected in patients who have an excision through the perilesional reactive zone when no effective adjuvant treatment was administered.

Wide margins are desirable for a few recurrent stage-3 benign bone tumours and for most bone and soft tissue sarcomas when the margins have been adequately defined by contemporary staging techniques, such as magnetic resonance imaging or computed tomography. Before the introduction of adequate imaging techniques and adjuvant

treatments, wide margins often were associated with a high rate of recurrence because of poor preoperative definition of the location and histological extension of the tumour. Radical resections, formerly the procedure of choice for most high-grade sarcomas, are now reserved for recurrent sarcomas after a pathological fracture through the bone sarcoma or when the margins cannot be defined accurately. Radical resections therefore are infrequently used for musculoskeletal sarcomas at the present time<sup>2,8</sup>

### Limb-sparing surgery for patients with sarcomas

Limb-sparing surgery for patients with primary malignant sarcomas of the extremities is now well established. MRI and CT now provide accurate tumour definition and enhance the possibility of achieving safe surgical margins. The first objective of this type of tumour surgery is to avoid local recurrence, which almost always leads to death. The second objective is to preserve as much function as possible. Amputation may be the only safe surgical option in some patients with extensive skin or neurovascular involvement: a 10% to 15% amputation rate is common.<sup>8</sup> Bony defects created by limb-sparing procedures may be reconstructed by any of a variety of methods. The options for reconstruction of large defects may be classified as biological, non-biological or combined. Biologic reconstructions using allografts or vascularised / non-vascularised autogenous grafts have given good results in diaphyseal defects. Osteoarticular reconstruction using allograft has been less successful. Large osteoarticular defects can be replaced by custom-made prostheses with mobile joints. The combination of allograft and prosthesis

as a composite is an option and its results are similar to that of endoprosthetic replacement. In some situations, arthrodesis using large spanning bone grafts may be appropriate. Intercalary segments of long bones may be filled with autograft (vascularised or non-vascularised), allograft or with custom-made implants. Distraction osteosynthesis may be considered when possible. Said and El-Sherif from Egypt reported a method of shortening and distraction for bridging bony defects created by *en-bloc* resection for two patients with tumours of the distal femur [8-10].

In growing children, limb-sparing surgery needs special consideration to avoid later limb-length discrepancy, and expandable prostheses have been developed to anticipate this problem. It is often necessary to sacrifice a major physis when the tumour is excised and the severity of limb-length discrepancy after excision of a major growth plate depends on the patient's bone age. Extendable prostheses are required when the estimated leg-length discrepancy at skeletal maturity is more than 3 cm or when the arm-length discrepancy is more than 5 cm. When the estimated discrepancy is less these patients can be treated with conventional "adult-type" prostheses made longer by up to 1.5 cm in the lower limb and 2 to 3 cm in the humerus. Complications include infection, local recurrence, aseptic loosening, joint stiffness, subluxation, periprosthetic fracture, and outgrowing the prosthesis. The introduction of non-invasive extendable prostheses is expected to significantly reduce the problems associated with multiple operations and infection<sup>11</sup>

A realistic estimate of the expected

function after a proposed limb-sparing procedure must be given preoperatively to patients and their relatives. All current methods have advantages and disadvantages. Allografts may be progressively incorporated by the host. Disadvantages include bone graft fractures and resorption, cartilage degeneration, joint instability, delayed union or non-union and the incidences are directly related to the size of the graft and the use of chemotherapy. Another major concern is the possibility of disease transmission. Prosthetic replacement has the advantages of allowing early weight bearing, having predictable function, having low risks of early complications and being readily available. The prostheses are expensive and complications are expected to increase with time. An arthrodesis is less attractive initially, but once it is achieved it provides a stable limb and avoids the complications associated with prosthetic replacement such as fracture, loosening and infection. The choice of reconstruction after distal femoral resection depends on the surgeon's personal experience and the availability of various techniques.<sup>8-10</sup> The evaluation and comparison of the various types of limb-sparing procedures are difficult, but Enneking's surgical staging system allows standardised preoperative evaluation, analysis and end-result reporting. The key to appropriate management of skeletal tumours lies in early detection, diagnosis, accurate staging and a multidisciplinary approach with surgical excision, (providing adequate tumour free margins) being the cornerstone.

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### Brain surgery

**B**rain surgery is perhaps the oldest of the practiced medical arts. No hard evidence exists suggesting a beginning to the practice of other facets of medicine such as pharmacology- using drugs, chemical and natural ingredients to help a fellow human being. There is ample evidence, however, of brain surgery, dating back to the Neolithic (late Stone Age) period. Unearthed remains of **successful** brain operations, as well as surgical implements, were found in France— at one of Europe’s noted archeological digs. And, the success rate was remarkable, even circa 7,000 B.C. But, pre-historic evidence of brain surgery was not limited to Europe. Pre-Incan civilization used brain surgery as an extensive practice as early as 2,000 B.C. In Paracas, Peru, a desert strip south of Lima, archeologic evidence indicates that brain surgery was used extensively. Here, too, an inordinate success rate was noted as patients were restored to health. The treatment was used for mental illnesses, epilepsy, headaches, organic diseases, osteomyelitis, as well as head injuries. Brain surgery was also used for both spiritual and magical reasons; often, the practice was limited to kings, priests and the nobility. Surgical tools in South America were made of both bronze and man-shaped obsidian (a hard, sharp-edged volcanic rock).

Africa showed evidence of brain surgery as early as 3,000 B.C. in papyrus writings found in Egypt. “Brain,” the actual word itself, is used here for the first time in any language. Egyptian knowledge of anatomy may have been rudimentary, but the ancient civilization did contribute important notations on the nervous system. Hippocrates, the father of

modern medical ethics, left many texts on brain surgery. Born on the Aegean Island of Cos in 470 B.C., Hippocrates was quite familiar with the clinical signs of head injuries. He also described seizures accurately, as well as spasms and classified head contusions, fractures and depressions. Many concepts found in his texts were still in good stead two thousand years after his death in 360 B.C.

Ancient Rome in the first century A.D. had its brain surgeon star, Aulus Cornelius Celsus. Hippocrates did not operate on depressed skull fractures; Celsus often did. Celsus also described the symptoms of brain injury in great detail. Asia was home to many talented brain surgeons: Galenus of Pergamon, born in Turkey, and the physicians of Byzance such as Oribasius (4th century) and Paul of Aegina. An Islamic school of brain surgery also flourished from 800 to 1200 A.D., the height of Islamic influence in the world. Abu Bekr Muhammed el Razi, who lived from 852 to 932 in the Common Era, was perhaps the greatest of Islamic brain surgeons. A second Islamic brain surgeon, Abu l’Qluasim Khalaf, lived and practiced in Cordoba, Spain, and was one of the great influences on western brain surgery.

The Christian surgeons of the Middle Ages were clerics, well educated, knowledgeable in Latin, and familiar with the realm of medical literature. Despite the church’s ban on study of anatomy, many churchmen of great renown (advisors and confessors to a succession of Popes) were outstanding physicians and surgeons. Leonardo Davinci’s portfolio containing hundreds of accurate anatomical sketches indicates the intense intellectual interest in the workings of the human body despite the Church’s ban.



# Gastric Cancer

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Review  
article

The gloomy view mentioned in = the title of this article still prevails in most parts of the world. However in the past few decades, a lot of changes in our understanding of this cancer have taken place. These

throughout the world. There are large differences in the incidence of this cancer in different parts of the world (fig. 1). Japan, Chile, Costa Rica, Ireland and east European countries record a high incidence rate whereas North America,

Western Europe and Australia are region of low incidence. Indian cities like Chennai and Bangalore record a high incidence (20-30/100,000 males) whereas in other cities like Mumbai, Delhi and Bhopal, the incidence is much lower (fig. 2). From Thrissur and northern parts of Kerala, higher number of cases is reported annually in the hospital statistics.

## Age and sex

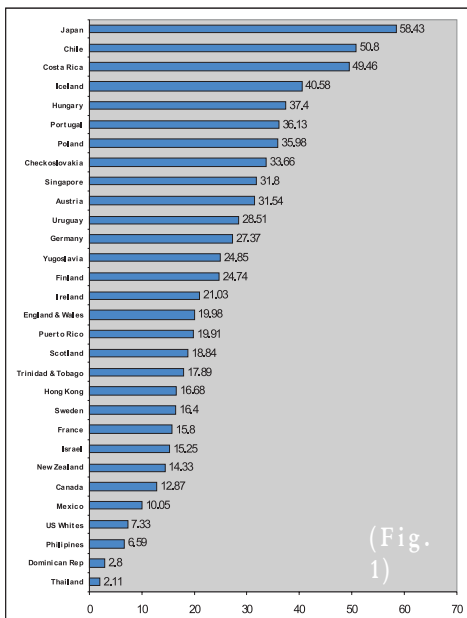
Maximum incidence is in the fifth and sixth decades. Male to female sex ratio is 2:1 throughout

the world. In younger age the ratio approaches unity. Of the histological types, the diffuse type is more common in younger age group.

## Trends

Throughout the world during the second half of last century, there was a declining tendency of gastric cancer mortality, the maximum being noticed at North America, where there is a reduction of 40-50%. In Japan, there was a decline of

only 8-12%, that too due to the early detection and treatment of gastric carcinoma (fig.3). The declining tendency throughout the world is for the

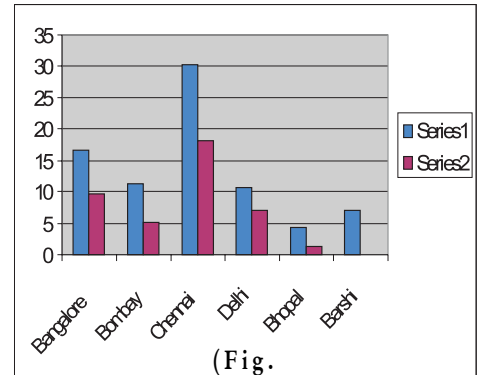


(Fig. 1)

changes include the epidemiological aspects, the role of Helicobacter pylori as a carcinogen, the developments of molecular biology of the cancer, the value of early detection and realisation of the importance of staging and aggressive surgical management. All these aspects are highlighted in this article.

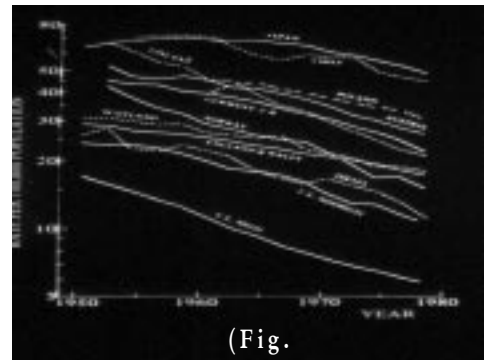
## Epidemiology

Gastric cancer is the second commonest cause of cancer mortality in the male



(Fig. 2)

distal gastric cancer, but the proximal gastric cancer seems to be increasing especially in the west.



(Fig. 3)

## Migrant studies

Studies of Japanese migrants to USA showed a relatively slow fall in mortality from gastric cancer in the first generation, but the rate drops sharply in the Japanese offspring's born in USA.

This data support two conclusions. Firstly, the influence of environment must be significant in the reduction of incidence in the second generation. Secondly, the risk is determined by patterns of exposure of environmental factors occurring early in life, as evidenced by stability of rates occurring among the first generation of Japanese migrants to USA.

### Dietary factors

Stomach being the organ of constant contact with contents of the diet, all epidemiological studies has been directed to find out the association of various food contents and risk of gastric carcinoma. The diet contents might act as a direct carcinogen, a promoter and even as an inhibitor. The association of nitrates and nitrites in the diet and water has been extensively investigated and found to be a significant risk factor. Nitrosamine is formed inside the stomach from nitrites and nitrates by bacteria. Nitrosamines are potent carcinogenic agents. Formation of nitrosamine in the stomach is inhibited by ascorbic acid and perhaps by other antioxidants. Other dietary factors like high salt intake, Smoked food, low protein intake and low consumption of fruits and vegetables, consumption of large quantity of spices are incriminated as etiological factors. The high risk factors observed from our own dietary survey include high consumption of dry salted fish, low intake of leafy vegetables and fruits and high intake of chilly. Strangely enough pan-chewing has been noticed as a high risk factor in our study<sup>1</sup>

### Helicobacter pylori (H.Pylori)

During the last two decades it has been established that H.pylori has a definite role in the pathogenesis of gastric adenocarcinoma and lymphoma.

Eurogast study group examined the relationship between the organism and gastric cancer in 17 populations from 13 countries. This showed a statistically significant relationship between seropositivity for H. pylori and cumulative incidence of gastric cancer in these populations. There was approximately six fold increase of gastric carcinoma in this population with H.pylori infections<sup>2</sup>. Forman et al have shown significant correlation between H.pylori infection and gastric cancer mortality in china<sup>3</sup>. Naomi Uemura et al in their recent prospective study of 1526 Japanese patients showed that gastric cancers developed in 36 (2.9%) of the H. Pylori infected and none of the uninfected patients<sup>4</sup>. Those with histological findings of severe gastric atrophy, corpus predominant gastritis or intestinal metaplasia are at increased risk. In 1994 the World Health Organization and International Agency for cancer consensus groups have accepted that there was sufficient epidemiological and histological evidence to classify H.pylori as a definite carcinogen<sup>5</sup>.

H.Pylori is a gram negative spiral shaped, microaerophilic, urease positive bacillus surviving in one of harshest environments of the human body, viz gastric acidity. It chronically infects the stomach over half of world's population. The infection is acquired during childhood via oral or faecal route and if not treated with antibiotics, it will persist throughout life.

H.Pylori infection results in three phenotypes of gastritis

- Mild pan gastritis- commonest and not associated with human disease.
- Corpus predominant gastritis which lead on to gastric atrophy and

intestinal metaplasia and gastric cancer.

- Antral predominant gastritis associated with increased gastric acid and duodenal ulcer. These patients will have an increased parietal cell mass. Probably the genotype of H.pylori which produces this type of gastritis is different from that producing gastric cancer.

Recently it has been demonstrated that the genotypes, H.Pylori Cag A +, Vac A are associated with gastric atrophy and intestinal metaplasia<sup>6,7</sup>.

### Intestinal metaplasia (IM)

There are three subdivisions of intestinal metaplasia. Type I or complete IM is characterized by the presence of absorptive cells, paneth cells and goblet cells secreting sialomucins (small intestinal type). Type II and type III are characterized by the presence of varying amount of columnar and goblet cells secreting sialomucin and/ or sulphomucins.

Type II secretes neutral and acid sialomucin

Type III secretes sulphomucins (Colonic IM)

Type III IM is associated with a four fold increased risk of gastric cancer. It is difficult to differentiate between these types of IM from endoscopic biopsies. Overall risk of gastric cancer in people with all types of IM is 10 fold. IM of the lesser curvature extending from the cardia to the pylorus or entire stomach is associated with a higher risk of gastric cancer.

### Other precursor conditions of gastric carcinogens

Prior gastric surgery- Balfour first

reported a correlation between prior gastric surgery for benign disease and subsequent development of gastric cancer in 1922. However the risk is observed only after a latency of 15 years and that too following partial gastrectomy for benign conditions

**Pernicious anaemia-** Patients with pernicious Anaemia are also at increased risk for developing gastric cancer. It is an auto immune disease associated with atrophic gastritis and subsequent IM. The relative risk for a patient with pernicious Anaemia developing gastric cancer is approximately 2.1 to 5.6

**Gastric polyps-** The presences of gastric polyps can increase a patient's risk of gastric cancer. Adenomatous polyps carry a definite risk for development of malignancy as in the case of colonic adenomatous polyps. The risk is approximately 10 to 20 % and increases with increasing size of the polyp. Endoscopic removal is indicated for pedunculated lesion and is sufficient if polyp is completely removed and if there are no foci of invasive cancer on histologic examination. If the polyp is larger than 2 cm or sessile or has a proven focus of invasive carcinoma, then operative excision is warranted.

Hyperplastic polyps are very common and are

considered as benign. However, their presence is associated with an increased risk of gastric cancer, because they form in stomachs with established gastritis, a known risk factor for carcinoma.

### Familial factors

There is a two to four fold increase of gastric cancer among the first degree relatives of the affected. Persons with blood group A have an approximate 20% relative risk of developing gastric cancer. Hanzel et al observed that this increased risk with blood group A is seen in diffuse

histology type<sup>8</sup>.

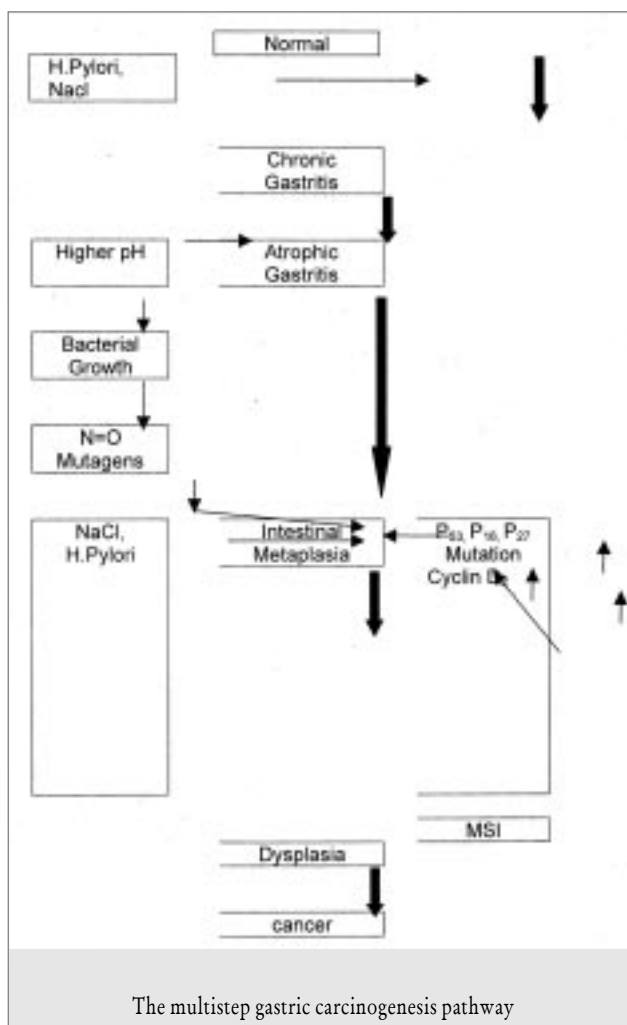
### The Molecular biology of gastric cancer

In contrast to colo-rectal cancer, the molecular biology of gastric cancer is less well worked out. The genetic alteration associated with gastric carcinoma can be classified as over expression / amplification of oncogenes and growth factor, inactivation of the Tumour suppressor genes, the reduction of cellular adhesion, and the reactivation of the telomerase and the presence of microsatellite instability.

The over expressed/ amplified oncogenes include c-Met, k-sam and c-erbB2. Similarly several growth factors like transforming growth factor alpha (TGF- $\alpha$ ), the epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF) are over expressed.

The inactivation of the Tumour suppressor genes P53 and P16 have been reported in both diffuse and intestinal type cancers, whereas adenomatous polyposis coli (APC) gene and beta-catenin gene mutations are frequent in intestinal type cancers.

Reduced cell adhesiveness is considered indispensable for both early and late carcinogenic steps. E-Cadherin (120kDa,



The multistep gastric carcinogenesis pathway

chromosome 16q) is a key functional component of adherence junction between epithelial cells. E-cadherin is bound via series of undercoat proteins, the catenins to the cytoskeleton. An intact E-cadherin – catenin complex is required for normal intercellular adhesion. The reduction of E-cadherin expression is found in approximately 50% of diffuse gastric cancers. The E-cadherin gene (CDH1) has been categorized as a tumor suppressor gene. Mutation of this gene has been implicated in diffuse gastric cancer.

**Microsatellite instability-** The human genome is punctuated with repetitive di, tri or tetranucleotide sequences termed microsatellites. Slippage during DNA replication is normally corrected by mismatch repair system. Deficiencies in this mismatch repair system results in microsatellite instability which is seen in approximately, 20 – 30 % of intestinal type of sporadic gastric cancer. This microsatellite instability is seen in virtually all hereditary non polyposis colo-rectal cancers

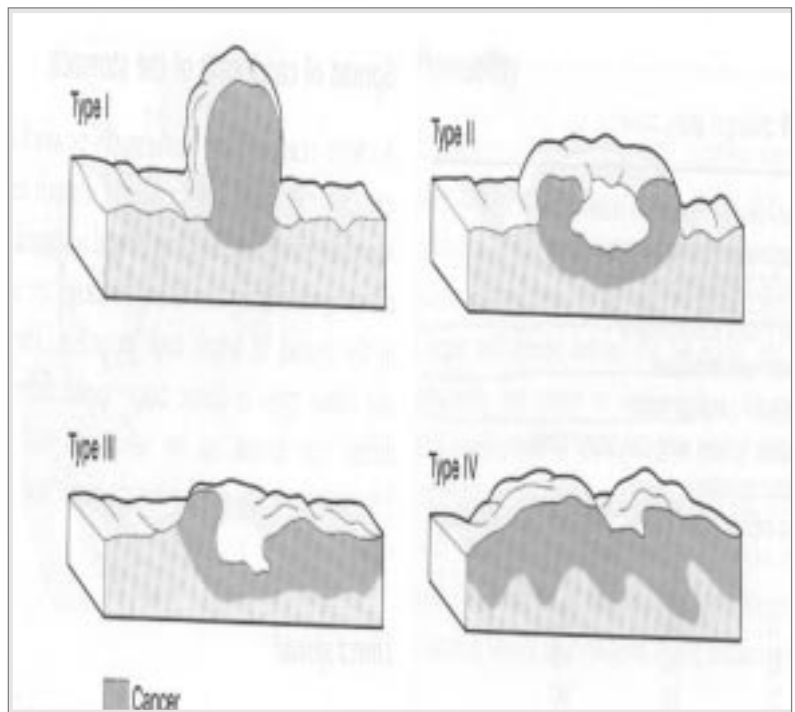
Correa and colleagues proposed a model for pathogenesis of intestinal type of gastric carcinoma as early as 1975 which is based on progression from gastritis to carcinoma over the course of several decades<sup>9</sup>. Recent evidences of role of H.pylori and advances in molecular biology highlights the role of these factors in the multistep wise progression of carcinogenesis apart from role of environmental factors like diet<sup>10</sup>.

The multistep gastric carcinogenesis pathway

### Pathology

Ninety five percent of gastric neoplasms are adenocarcinomas.

Macroscopic Appearance of advanced Carcinoma



The Borrmann's classification system (fig-4)

- Type I Polypoid or fungating lesions
- Type II Ulcerating lesions surrounded by elevated borders
- Type III Ulcerating lesion infiltrating into the gastric wall
- Type IV Diffusely infiltrating lesions
- Type V Unclassified

### Histology

Many histological classifications of gastric adenocarcinomas have been proposed. The most popular and useful system is proposed by Lauren<sup>10</sup> in 1965. This classification separates gastric cancer into intestinal and diffuse types with different pathology, epidemiology, pathogenesis and prognosis. The Correa hypothesis of gastric carcinogenesis is proposed for the intestinal type which arises from the precancerous condition

gastric atrophy and intestinal metaplasia.

Distinctive features of the two histological types of Lauren's classification are as follows:

Intestinal	Diffuse
Environmental	Familial Blood group A
Gastric atrophy	
Intestinal metaplasia	
Men > Women	Women > Men
older age group	younger age group
Gland formation (well differentiated)	Poorly differentiated, signet ring cells
Haematogenous	Transmural/Lymphatic spread
Micro satellite instability	Reduction of E.cadherin expression
APC gene mutation	
P53, P16 inactivation	P53, P16 inactivation

## WHO classification

In 1990 the world Health Organization recommended another classification system for gastric cancers. According to this system, carcinoma of the stomach is divided into adenocarcinoma, adenosquamous carcinoma, squamous celled carcinoma, undifferentiated carcinoma and unclassified carcinoma, Adenocarcinomas are further divided into: papillary, tubular, mucinous and signet ring. Each type is further subdivided by degree of differentiation

## Diagnosis and staging of gastric cancer

The early diagnosis of gastric carcinoma is difficult in most countries except in Japan where screening investigations detect more than 50% of early gastric cancers. Gastric adenocarcinoma lacks specific symptoms early in the course of the disease. Dyspeptic symptoms like vague epigastric discomfort and indigestion are mistaken for gastritis or ulcer disease and resort to symptomatic treatment without diagnostic investigations for a variable period. Typically the pain is constant, non radiating and unrelieved by food ingestion. More advanced disease may present with weight loss, anorexia, fatigue or vomiting. Proximal tumors often presents with dysphagea, whereas distal antral tumors present with gastric outlet obstruction. Diffuse mural involvement by Tumour, as occurs in linitis plastica, leads to decreased distensibility of the stomach and early satiety. 15% may present with haematemesis and 40% are anemic at the time of presentation. Very large tumors may erode into transverse colon presenting with large bowel obstruction.

Physical signs include palpable epigastric

mass, palpable supraclavicular (Virchow's) or periumbilical (Sister Mary Joseph's) lymph nodes, peritoneal metastasis palpable by rectal examination (Blumer's shelf) or palpable ovarian mass (Krukenberg's Tumour). As the disease progress, patients may develop hepatomegaly secondary to metastasis, jaundice, ascites and cachexia.

## Investigation

1. Flexible Upper GI endoscopy & biopsy is preferable to upper GI radiology with double contrast barium. The addition of direct brush cytology to multiple biopsies increases the diagnostic accuracy.

2. Endoscopic ultra sonography (EUS) assists in the staging of the disease viz extent of gastric wall invasion as well as nodal station

3. Complete Blood count, serum chemistries including liver function tests, coagulation studies, chest X-ray and CT scan of abdomen & pelvis, CT scan of chest for proximal gastric cancer are needed for staging and further management

4. Laparoscopy: Laparoscopy can detect metastatic diseases of smaller size not detected by CT scan in 23% to 37% of patients

Cytological analysis of peritoneal fluid or fluid obtained by peritoneal lavage may reveal the presence of free intraperitoneal gastric cancer cells. Patients with positive findings on peritoneal cytology have a poor prognosis, similar to macroscopic stage IV disease.

## Staging of gastric carcinoma

Two major staging systems are TNM staging system & JRSGC staging system of Japanese Research Society.

## TNM Staging (1997)

A major revision occurred in 1997 when nodal status stratification was changed in the fifth edition of TNM classification. In this staging system, a minimum of 15 lymph nodes must be evaluated for accurate stage

## T. Primary tumour

T<sub>0</sub> - No evidence of primary Tumour

T<sub>is</sub> - Tumour limited to mucosa, no penetration of the basement membrane

T<sub>1a</sub> - Limited to mucosa with invasion of lamina propria

T<sub>1b</sub> - Tumour invades submucosa

T<sub>2 a</sub> - Tumour invades muscularis propria

T<sub>2b</sub> - Tumour invades subserosa

T<sub>3</sub> - Penetration of serosa without invasion of adjacent tissues

T<sub>4</sub> - Invades adjacent tissues and / organ

## N. Category

In 1997 staging, nodal status is based on the histopathologically involved nodes

PN<sub>0</sub> : No metastatic lymph nodes

PN<sub>1</sub> : Involvement of 1-6 metastatic nodes

PN<sub>2</sub> : Involvement of 7 - 15 metastatic nodes

PN<sub>3</sub> : Involvement of > 15 metastatic nodes

The definition of "regional nodes" includes perigastric nodes and nodes along the left gastric, common hepatic, splenic and coeliac arteries and hepatoduodenal ligament (1-12 according to JRSGC). The involvement of other nodes such as retro pancreatic, mesenteric and Para aortic nodes (13-16, according to JRSGC) is classified as distant metastasis (M1)

## M - Category

Mo – No metastasis to distant organs

M1 – Distant metastasis present. Also metastasis to the distant lymph nodes as mentioned above and peritoneal metastasis

Mx – Distant metastasis cannot be assessed

### Stage grouping according to TNM staging

Stage : Tis No Mo

Stage Ia : T1No Mo

Stage Ib : T1N1Mo, T2 No Mo

Stage II : T1 N2 Mo, T2 N1 Mo, T3 No Mo

Stage IIIa : T2 N2 Mo, T3 N1 Mo, T4 No Mo

Stage IIIb : T3 N2 Mo, T4 N1 Mo

Stage IV : T4 N2 Mo, Any T, Any N, M1

### Japanese Research Society for Gastric Cancer (JRSGC) classification system (13<sup>th</sup> Edition)<sup>11</sup>

The principles of JRSGC staging depend on

1. Clinical findings (c)
2. Surgical findings (s)
3. Pathological findings (p)
4. Final findings (f)

**Clinical findings-** Any findings during diagnostic evaluation, including laparoscopy, are defined as clinical findings. These are recorded as Ct2, cN1, cM0, c stage II

**Surgical findings-** Any findings during surgery including frozen sections, cytology and macroscopic examination of the resected specimens are defined as

surgical findings Results of therapeutic laparoscopy are included in surgical findings.

**Pathological findings-** Any findings based on microscopic examination of materials obtained by endoscopic, laparoscopic or surgical resection are defined as pathological findings.

**Final findings-** Comprehensive findings based on clinical, surgical and pathological findings are defined as final findings. When there is conflict between surgical and pathological findings, the pathological findings take precedence.

### A. Primary lesions

1. Number and size of lesion – two largest dimensions should be recorded for each lesion.

2. Tumour location

U- Upper third	} 3 portions of the stomach
M- Middle third	
L – Lower third	
E – Esophagus	} Tumour extension
D – Duodenum	

Four equal parts of the circumference –

Less: - lesser curvature,

Gre: - Greater curvature

Ant: - Anterior wall

Post: - Posterior wall

### 3. Macroscopic types

Type 0 - Early gastric cancer (T1 of TNM)

Sub classified into

Type 0I : Protruded type

Type 0II a : Superficial elevated type

Type 0IIb : Flat type

Type 0IIc : Superficial depressed type

Type 0III : Excavated type

Type I : Polypoids, Sharply demarcated from the surrounding mucosa, usually attached on a wide base.

Type 2 : Ulcerated carcinomas with sharply demarcated and raised margins

Type 3 : Ulcerated carcinomas without definite limits, infiltrating into the surrounding wall

Type 4 : Diffusely infiltrating carcinoma in which ulceration is usually not a marked features

Type 5 : Non- classifiable carcinoma that cannot be classified into any of the above types.

Type 1 to 5 is similar to Borrmann's classification

### 4. Depth of tumor invasion (T)

T1 : Tumor invasion of mucosa and /or muscularis mucosa (M) or submucosa (SM)

T2 : Tumor invasion of muscularis propria (MP) or subserosa (SS)

T3 : Tumor penetration of Serosa (SE)

T4 : Tumor invasion of adjacent structures ( S I )

Tx : Unknown

### B. Metastatic lesions

1. Lymph node Metastasis

Regional lymph nodes are numbered by JRSGC as follows

No.1 Right Paracardial lymph nodes (LN)

No.2 Left Paracardial LN

No.3 LN along the lesser curvature

No.4sa LN along the short gastric vessel

No.4sb LN along the right gastroepiploic vessels

- No 5 Suprapyloric LN
- No 6 Infrapyloric LN
- No 7 LN along the left gastric artery
- No 8a LN along the common hepatic artery (antero superior group)
- No 8p LN along the common hepatic artery (posterior group)
- No 9 LN around the celiac artery
- No 10 LN at the splenic hilum
- No 11p LN along the proximal splenic artery
- No 11d LN along the distal splenic artery
- No 12a LN in the hepatoduodenal ligament (along the hepatic artery)
- No 12b LN in the hepaoto duodenal ligament (along the bile duct)
- No 12p LN in the hepatoduodnal ligament (behind the portal vein)
- No 13 LN on the Posterior surface of the pancreatic bed
- No 14v LN along the superior mesenteric vein
- No 14a- LN along the superior mesenteric artery
- No 15 LN along the middle colic vessels
- No 16a1 LN around the aortic hiatus
- No 16a2 LN around the abdominal aorta (from the upper margin of the celiac trunk to the lower margin of the left renal vein)
- No 16 b1 LN around the abdominal aorta (from the lower margin of the left renal vein to the upper margin of the inferior mesenteric artery)
- No 16b2 LN around the abdominal aorta (from the upper margin of inferior mesenteric artery to the aortic bifurcation)
- No 17 LN on the anterior surface of the pancreatic head
- No 18 LN on the inferior margin of the pancreas
- No 19 Infradiaphragmatic lymph nodes
- No 20 LN in the esophageal hiatus of the diaphragm
- No 110 Para esophageal LN in the lower thorax
- No 111 Supradiaphragmatic LN
- No 112 Posterior mediastinal LN.
- The detailed classification of the lymph nodes depending on the location of the Tumour is available JRSGC classification – 13<sup>th</sup> edition. N4 group has been classified as metastatic disease in the 13<sup>th</sup> edition

## 2. Liver metastasis (H)

Ho – No liver metastasis

H1 – liver metastasis

Hx – unknown

## 3. Peritoneal metastasis (P)

Po, P1, PX

### 1. Peritoneal cytology ( Cy)

CY0, CY1, CYX

### 2. Other distant metastasis( M)

Mo, MI, Mx

MI should be categorized according to the following notation.

LYM – Lymph nodes

PUL – Pulmonary

PLE – Pleura

MAR – Bone Marrow

OSS – Osseous

BRA – Brain

MEN – Meninges

OTH – Others

### C. stage grouping

	No	N1	N2
N3			
T1	IA	IB	II
T2	IB	II	IIIA
T3	II	IIIA	IIIB
IV			
T4	IIIA	IIIB	IV
H1,P1,Cy1,M1	IV		

## Surgical treatment

### Early gastric carcinoma (EGC)

EGC is a unique form of gastric carcinoma confined to mucosa and submucosa (TNM – T1, JRSGC Type 0) irrespective of the involvement of lymph nodes. It has an excellent prognosis. Aggressive screening practice in Japan resulted in detection of EGC in more than 50% cases of total number of cases. Node positive patients with EGC have a significantly poorer survival rate than node negative patients. The overall incidence of metastasis in lymph nodes in EGC is 5.7% to 13%; for mucosal carcinomas – 1.2 to 2.6% and submucosal carcinomas – 16.5% to 23.8%. Younger age group, macroscopic depressed type, large tumor size (> 30mm), undifferentiated histologic type, histologic ulceration of carcinoma and lymphatic vessel invasion have a significant association with regional lymph node metastasis.

**Surgical decision making in EGC**  
(Recommendations of Japanese Gastric cancer Association March 2001)<sup>12</sup>

## Mucosal Cancer (M)- No

Differentiated -  $\leq 2\text{cm}$   
—————► Endoscopic mucosal  
Resection (EMR)

Not differentiated - Modified  
Gastrectomy A (MGA)

(MGA =  $\frac{2}{3}$  gastrectomy + D1-N1 node  
dissection + No.7 node dissection)

Submucosal (SM)-No

Differentiated  $< 1.5\text{cm}$ - MGA

Not differentiated -MGB ( $\frac{2}{3}$   
gastrectomy + D1 + No.7, 8a & 9 - node  
dissection)

Modified Gastrectomy could be vagus  
preserving, pylorus preserving or  
laparoscopic

Surgical treatment of more advanced  
stage of gastric cancer as recommended  
by Japanese Gastric Cancer Association  
- March 2001

Stage IB - T1 N1 (EGC), T2 N0

T1 (M, SM)  $< 2\text{cm}$  N1 - Modified  
Gastrectomy B (MGB)

T1 (M, SM)  $> 2\text{cm}$  N1 - Standard D2  
T2 (MP, SS) No - Standard D2

D2 dissection means dissection of group  
N1 & N2 lymph nodes (as Per JRS GC)

Stage II

T1 N2, T2 N1, T3 N0 - standard D2

Stage III A

T2 N2 T3 N1 - Standard D2

T4 No - Extended resection including  
involved adjacent organs + Adjuvant or  
neoadjuvant chemotherapy, because of  
the chance of R1 surgery (R1 =  
microscopic Residual tumor present)

Stage IIIB

T3 N2 - Standard D2 or D3

T4 N1 - Extended Resection

Adjuvant chemotherapy, neoadjuvant  
chemotherapy and adjuvant radiotherapy

should be given in the setting of  
randomized control trial.

Stage IV

Most cases of stage IV cancer cannot be  
curatively treated with surgery alone. If  
N3 is the only determinant factor for  
stage IV, D3 surgery may have a potential  
for R0 dissection.

D3 dissection means dissection of the  
groups N1, N2 and N3 lymph nodes

R0 surgery means no microscopic  
residual Tumour after dissection.

In patient with M1 lesion, but with good  
performance status, chemotherapy and /  
or radiotherapy with palliative resection  
give the best supportive care.

The palliative surgery such as resection,  
bypass, gastrostomy or jejunostomy may  
be indicated in patients with urgent  
symptoms like bleeding, stenosis and  
malnutrition.

### Surgical approaches

Intraluminal endoscopy (for  
mucosectomy)

Laparoscopy / combined laparoscopy  
and Intra luminal endoscopy

Laparotomy

Thoraco- laparotomy

### Operative procedure

Mucosectomy

Wedge resection

Segmental resection

Proximal gastrectomy

Pylorus preserving gastrectomy

Distal gastrectomy

Total gastrectomy

### Controversy regarding the radical lymphadenectomy

It has always been a question why  
Japanese results of surgical treatment of  
gastric carcinoma are better. There are

different explanations for this question  
1) it is due to early pick up of the disease  
2) Japanese gastric cancer is biologically  
different disease 3) In Japan, a higher  
proportion of patients with good  
prognostic features are seen than in the  
west . There is no definite evidence to  
support these arguments.

In all stage of gastric carcinoma the  
Japanese results are much superior to the  
western results .In carcinoma stomach  
stage II, survival in USA is 29% - 30 % , in  
Germany 43.7% - 45% while in Japan it  
is 71.7 % - 75%, for stage IIIA survival is  
15% in USA, 28.6 - 30% in Germany  
and 47.7.- 60% in Japan. A combination  
of differences in staging and a higher  
standard of surgery in Japan probably  
accounts for the differences. Staging is  
crucial when survival figures are  
compared. The more thorough the  
staging, the higher stage is likely to be,  
and therefore, stage for stage, the  
outcome seems better in patients who are  
adequately staged pathologically. This  
phenomenon is called 'stage migration'  
(Will Roger's phenomenon). The  
pathologist will have difficulty  
orientating a fixed specimen, hence  
optimal approach is for the surgeon to  
dissect the lymph nodes and label before  
sending to the pathologists . This practice  
is being followed in Japan.

However, the better survival benefits of  
D2 dissection for early stage carcinomas  
could not be reproduced by the  
randomized control studies of the west,  
especially the MRC trial of UK and  
Dutch gastric cancer group study<sup>13,14</sup>.  
There was no survival benefit for D2  
dissection by these studies and was  
associated with increased rate of  
morbidity and mortality. But other  
western studies report less morbidity and  
mortality with D2 dissection<sup>15,16,17</sup>. The  
increased morbidity and mortality  
associated with D2 surgery is considered



to be due to the complications of distal pancreatectomy and splenectomy. Hence the recent trend even by Japanese doyens like Maruyama is to preserve tail of pancreas and spleen during D2 dissection, unless these structures are infiltrated by the tumor<sup>18,19</sup>. That is why in the 13<sup>th</sup> edition, a more tailored approach to the surgical treatment of gastric cancer was recommended by JRS GC

### Conclusion

- Gastric cancer is one of the most lethal and common cancers of the world. Except in Japan where population based screening programme is available, this cancer is detected in an advanced stage and hence prognosis is dismal for this cancer. Therefore it is known as the captain of men of death.
- There is a declining trend of distal gastric cancer all over the world, but the proximal gastric cancer seems to be increasing.
- A multistep process of oncogenesis involving dietary factors, Helicobacter pylori and genetic factors has been proposed. Modulation of this multifactorial process might result in the control and therapy of this disease in future.
- The staging system proposed by JRS GC is exhaustive, but meticulous in planning treatment strategies
- Although western surgeons do not advocate radical lymphadenectomy, the Japanese surgeons, with their extensive experience in this form of lymphadenectomy and consequent improved survival of gastric carcinoma patients, believe that a randomized controlled trial (RCT) of D2 dissection is unethical.

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### History of Surgery

The first surgical procedures were performed in the Neolithic Age (about 10,000 to 6000 BC). Trepanning, a procedure in which a hole is drilled in the skull to relieve pressure on the brain, may have been performed as early as 8000 BC. In Egypt, carvings dating to 2500 BC describe surgical circumcision—the removal of foreskin from the penis and the clitoris from female genitalia. Ancient Egyptian medical texts have been found that provide instructions for many surgical procedures including repairing a broken bone and mending a serious wound. In ancient India, the Hindus surgically treated bone fractures and removed bladder stones, tumors, and infected tonsils. They developed plastic surgery in 2000 BC. Using skin flaps from the forehead, Hindu surgeons shaped new noses and ears for the punished criminals. In the 4th century BC, the Greek physician Hippocrates published descriptions of various surgical procedures, such as the treatment of fractures and skull injuries.

During most of the Middle Ages (5th to 14th century AD), the practice of surgery declined and its practice was left to barbers who traveled from town to town cutting hair, removing tumors, pulling teeth, stitching wounds, and *bloodletting*, the

practice of draining blood from the body, then thought to cure illness.

In 1316 the French surgeon Guy de Chauliac published *Chirurgia magna* (Great Surgery). The text helped surgery gain respect as a serious science. At this time a new order of surgeons arose in France. They were called surgeons of the long robe, distinguished from the barber surgeons who were known as surgeons of the short robe. The barber surgeons had little medical training, while the surgeons of the long robe were studied physicians and considered such practices as bloodletting primitive. Corporations, or guilds, of surgeons of the long robe were formed in several countries.

During the 16th, 17th, and 18th centuries Much credit belongs to the French surgeon Ambroise Paré, often called the father of modern surgery. Paré successfully employed the method of ligating, or tying off, arteries to control bleeding, thus eliminating the old method of cauterizing, or searing, the bleeding part with a red-hot iron or boiling oil. The English physician and anatomist William Harvey discovered the process of blood circulation and Italian anatomist Marcello Malpighi identified the existence of tiny blood vessels called capillaries that carry blood from the major blood vessels to the cells of the body. John Hunter, a British anatomist and surgeon, performed many experimental operations that advanced the practice of surgery.

In 1846 anesthesia was used as a way to mask pain during surgery by American dentist William Morton. Although Morton is often credited with the discovery of surgical anesthesia, American surgeon Crawford Long used anesthesia in

1842 during the removal of tumors but did not publish his results until 1849.

Post-surgical infections remained a serious complication of surgery until the mid-19th century when the French chemist Louis Pasteur discovered that fermentation or *putrefaction*, the decay and death of body tissue, is caused by bacteria in the air. In 1865 the British surgeon Joseph Lister applied Pasteur's work to surgery, developing *antiseptic* (germ-killing) techniques including the use of a carbolic acid spray to kill germs in the operating room before surgery. These antiseptic procedures helped eliminate postoperative infection. Other physicians, including Austrian Ignaz Semmelweis and American Oliver Wendell Holmes, determined that bacteria are also carried on the hands and clothing and transferred from patient to patient as a physician attends one after another. These physicians pioneered techniques such as washing hands and changing into clean clothing before surgery that prevent wounds from being contaminated during surgery.

At the turn of the 20th century, improved diagnostic abilities and methods of treatment helped surgery become even more effective. When the German physicist Wilhelm Conrad Roentgen invented X ray in 1895 to "photograph" the inside of the body he changed the way surgery was performed. The discovery of the blood groups A, B, and O by Austrian pathologist Karl Landsteiner enabled surgeons to give patients transfusions of their own blood type to ensure survival during surgery.

The introduction of antibiotics in the 1940s further minimized the risk of postoperative infection.

# Hepato Cellular Carcinoma

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**H**epato cellular cancer is one of the most deadly and common cancers in the world. Its survival rate is miserably low, only 5% surviving in 5-year period. Incidence of the disease worldwide is increasing, so an Imageologist should have a knowledge about the pathogenesis, natural course of the disease, recent advances in early detection, when the tumor is at a treatable stage. The Imageologist should also have knowledge of treatment and the recurrence rate in the management of hepato cellular carcinoma

## Aetio -pathogenesis

The chronic inflammatory disease of any cause can potentially induce hepato cellular carcinoma. These diseases lead to cirrhosis, which ultimately is the precursor in 80% of the cases. However non-cirrhotic, non-viral causes can also induce hepato cellular carcinoma. Test for Hepatitis – B and Hepatitis C is mandatory at the diagnosis of hepato cellular carcinoma. Other causes have also to be kept in mind like alcohol, industrial pollutant, pharmaceutical, synthetic agents, aflatoxin, vinyl chloride, estrogens, androgens, anabolic steroids, hemochromatosis, alpha-antitrypsin, which can potentially induce the cancer. The male female ratio is 4 : 1

## Patient presentation

Patients usually present in the advanced stage of disease in India. As the disease is clinically silent until the tumor exceeds 10cms. or when there is a diffused

involvement and sudden decompensation of the liver. Most of the patients present with a paraneoplastic picture like erythrocytosis, hypoglycemia, hypercholesterolemia, carcinoid like picture

Effective screening programs will detect small tumors less than 2cms in diameter, failing which the detection is often late. Since there is no effective screening procedure in India and the natural course of the disease is clinically silent and manifest when tumor exceeds 10cm in diameter in India most of the patients present in the stage when there is diffuse involvement, or multicentric involvement with sudden decompensation.

## Diagnostic imaging appearances

These may be classified as early tumor detection i.e., screening method, imaging, staging after the clinical presentation of the late or an advanced stage of the disease process. Supportive laboratory test include blood cell count, blood chemistry, serum transaminase, albumin level, prothombin time, alpha – fetoprotein level that is mandatory in the diagnosis. Paracentesis and analysis of the aspirate is essential when ascites is present.

Screening methods adopted in west and Japan are different. The methods available are alpha fetoprotein levels, high-resolution ultrasound infusion hepatic angiography, Lipiodol CT scan some of the methods like. Infusion hepatic angiography is not used in the present day because of its invasive and is

replaced by multislice CT. Multiphase abdominal CT scan, which is now the imaging procedure of choice despite the high cost involved and availability in large cities only. An AFP level with ultrasound have a higher specificity and sensitivity and is able to detected at high rate of 80% and above. The variability in detection depends as it is operator dependent and local factors like obesity, gas in abdomen etc when the procedure have to be repeated to achieve greater sensitivity.

MRI plays a limited role and is less sensitive than angiographic assisted multiphase multi slice CT

Application and Limitation of Imaging Techniques

**Plain X-ray** is nonspecific may show enlarged liver if the mass is large and is palpable, calcification is rare in HCC, contrast deposition in liver and lymph nodes seen if prior exposure to the contrast material exists.

**Nuclear medicine:** Is non-specific and shows a cold defects if sulphur colloid is used and may show uptake in the mass if bile secreting with gallium. It shows a positive scan in 90% of the case.

**CT appearance:** Depends on the tumor size, multi centricity and diffuseness and the phase in which it is taken. In the unenhanced CT it is isodense if the mass is large central areas of necrosis may be seen. In the arterial phase it is hyper dense. In the portal venous phase it becomes isodense or hypo dense, delayed phase may show a capsule a more

specific sign of HCC. CT also helps in detecting portal venous involvement Hepatic vein involvement and bleeding within the tumour. In the scenario of a large tumor with the positive AFP level it suggest HCC, reliability suffers in small HCC as it can be confused with hepatic nodules. Lipiodol CT helps in detecting satellite nodules as Lipiodol accumulates within the tumor due to a macro leak a fact that is useful in targeting chemo embolic mixture in HCC

**MRI:** HCC appears as iso intense, hypo intense or hyper intense relative to the normal liver in T1 weighted images, In contrast, at T2 weighted, it appears hyper intense.

**Ultrasound:** the appearance depends upon the operator and is variable, small HCC may be difficult to detect if careful screening is not performed. Small HCC's are hyper echoic and mimic hemangioma as fat is present in large amount within the tumor, if correlated with AFP level it has high degree of sensitivity, in combination with the Doppler it is useful in detecting associated vascular abnormalities like portal vein involvement which is common in HCC, hepatic vein involvement is a more specific sign of HCC

**Interventional radiology:** A number of ablative procedures are available in the treatment of HCC, alcohol injection, acetic acid injection, interstitial laser, radio frequency ablation, micro wave therapy, cyroablation. Their usefulness depends upon the size, and proximity of the tumor to the vessels. The embolisation procedure, like chemoembolisation i.e., regional chemotherapy, bland embolisation of HCC by reducing its blood supply, and devascularisation which is helpful in symptomatic

improvement, but in no way effective in the improvement of long term survival. It can improve survival to a three year survival rate if detected early in size less than 3cm and especially if Ethanol or other ablative procedure are used which is cost effective and now can be widely practiced.

**Local ablation strategies:** Radio frequency ablation is a technique that uses heat to thermally ablate tumors. A thin probe (18 gauge) is inserted into the middle of the tumor, then needle electrodes are deployed to adjustable distances. An alternating electrical current (400 to 500 kHz) is delivered through the electrodes. The current causes agitation of the particles of the surrounding tissues, generating frictional heat. The heat leads to a reliable sphere of necrosis. The size of the sphere depends on the length of deployment of the electrodes. Currently, the maximum size of the probe arrays allows for a 7-cm zone of necrosis. This would be adequate for a 5-cm tumor. The heat reliably kills cells within the zone of necrosis. The lack of uniform success is due to the difficulty of positioning the probe accurately in three dimensions using ultrasonographic or CT guidance. Also, large blood vessels may act as heat sinks, preventing adequate cytodestruction of cells adjacent to these structures. Finally, treatment of tumors close to the main portal pedicles can lead to bile duct injury and obstruction. This limits the location of tumors that are optimally suited for this technique. In series examining the results of treatment of HCC with radio frequency ablation, the data suggest a uniformly excellent response, with a local recurrence rate (at the site of ablation) of between 5% and 20%. The treatment can be performed percutaneously with CT or ultrasonographic guidance, or at the time

of laparoscopy with ultrasonographic guidance. The disadvantage of the laparoscopic approach is the requirement for general anesthesia, but some have suggested better results with this approach. Use of the percutaneous approach may also be limited by the presence of structures at risk for injury around the tumor, such as the diaphragm, colon, or gallbladder. These structures can be retracted free in a laparoscopic approach. In general, radio frequency ablation is reliable as a single treatment. A single ablation can take up to 20 minutes for a 7-cm ablation. The procedure is well tolerated and can be performed on an outpatient basis. It can be repeated numerous times and frequently, especially if performed percutaneously. This technique is best-suited overall for small tumors (less than 3 cm) deep within the hepatic parenchyma and away from the hepatic hilum. Complete preservation of hepatic parenchyma is possible with reliable tumor killing. A theoretical risk of needle tract tumor seeding exists. The tract can be thermally ablated while retracting the needle, which decreases this risk.

**Local injection therapy:** Numerous agents have been used for local injection into tumors, but the most commonly used agent has been ethanol. Ethanol injection into HCC is the most widely used therapy worldwide. The relatively soft HCC within the hard background cirrhotic liver allows injection of large volumes of ethanol into the tumor without diffusion into the hepatic parenchyma or leakage out of the liver. Ethanol causes a direct destruction of cancer cells, but it is in no way selective for cancer and will destroy normal cells in the vicinity. The key to success is the accuracy of the injection. This technique

is associated with a 15% risk of recurrence at the site of treatment. It has the advantage of being minimally invasive, because a very small needle can be used for injection, and it is quite inexpensive. The disadvantage is that a response usually requires multiple injections (average of three). The maximum size of tumor that can be reliably treated is 3 cm, even with multiple injections. For this reason, radio frequency ablation is preferable to most clinicians. Nevertheless, the cost of radio frequency ablation may be prohibitive in many places. Acetic acid is another agent with established success as a local injection for HCC. A randomized trial suggested that local recurrence is lower with acetic acid than with ethanol.

**Regional chemotherapy:** Although the results of systemic chemotherapy for either regional or metastatic HCC are dismal, a large number of encouraging reports have appeared concerning a variety of regional chemotherapies for HCC confined to the liver. Despite the fact that increased hepatic extraction of chemotherapy has been shown for very few drugs, some drugs such as cisplatin, doxorubicin, mitomycin C, and possibly neocarzinostatin have been found to produce substantial objective responses when administered regionally. In contrast to the Western experience for metastatic colon cancer to the liver, few data are available regarding continuous hepatic arterial infusion for HCC, although pilot studies are suggestive. Almost all studies have been done using bolus administration. Many but not all of the studies on regional intrahepatic arterial chemotherapy also use an embolizing agent such as Lipiodol, gelatin (Gelfoam), starch (Spherex), microspheres, or polyvinyl alcohol

(Ivalon). The last is rarely used now, due to increased hepatotoxicity. Two new products have now come to market using microspheres of defined size ranges. They are Embosphere (BioSphere) and Contour SE (Boston Scientific). The optimal diameter of the particles for transcatheter arterial chemoembolisation (TACE) has yet to be defined. Consistently higher objective response rates are reported for arterial administration of drugs together with some form of hepatic artery occlusion than for any form of systemic chemotherapy to date.

### **Cholangiocarcinoma**

Cancers of the bile ducts are rare tumors. Because of the proximity of the bile duct to the liver, the pancreas, and major vascular structures, surgical excision of these tumors usually requires a major hepatic or pancreatic resection or both. Major vascular reconstructions may also be necessary. The technical demands of such resections and the lack of effective alternative therapies for cholangiocarcinomas explain the nihilistic attitude that generally surrounds this disease. Advances in imaging over the last two decades now allow for earlier diagnosis of bile duct cancer and better surgical planning.

### **Epidemiology and Etiology**

Cholangiocarcinoma is a disease of the elderly, with the majority of such lesions occurring in patients older than 65 years and the peak incidence occurring in the eighth decade of life. Untreated, bile duct cancers are rapidly fatal diseases, and the majority of patients will die within 6 months to a year of diagnosis. Death usually results from liver failure or biliary sepsis. Long-term survival is highly dependent on the effectiveness of surgical therapy. A number of are

associated with an increased incidence of cholangiocarcinomas, including PSC, choledochal cysts or Caroli's disease, and pyogenic cholangiohepatitis and other hepatic infections. In addition, environmental agents may influence the incidence of cholangiocarcinomas.

### **Distal bile duct cancers**

USG will demonstrate a dilated extra hepatic and intrahepatic biliary tree. Cross-sectional imaging by CT scanning will usually then demonstrate a mass in the region of the head of the pancreas.

### **Treatment options**

Complete resection is the only effective and potentially curative therapy for cancers of the lower bile duct. In patients with nonresectable cancers, palliation for biliary obstruction can be achieved with a surgical bypass or biliary endoprotheses. Endoprotheses for distal biliary obstruction are usually placed endoscopically and provide more durable palliation than does an endoprotheses placed for hilar obstruction. Surgical bypasses also provide excellent relief of jaundice and can be achieved with an acceptably low morbidity and mortality. All other patients are treated with biliary endoprotheses. Chemotherapy or radiotherapy or both have offered generally poor results as palliative treatment for unresectable cases. Survival beyond 1 year is uncommon in patients subjected to palliative therapies.

### **Proximal or hilar cholangiocarcinoma**

Proximal or hilar cholangiocarcinomas represent the greatest diagnostic and therapeutic challenge because of the vast number of vital structures that can be involved by even a small hilar cholangiocarcinoma. Proximal or hilar

cholangiocarcinomas require the most extensive of liver resections and vascular reconstruction for extirpation.

### **Radiographic evaluation**

Radiological imaging is central to the diagnosis and treatment planning for patients with cholangiocarcinomas. The importance of imaging studies results from the difficulties in obtaining a positive tissue diagnosis by biopsy, particularly when the tumors are small and in the potentially curable stages. Relying on the results of percutaneous needle biopsy or biliary brush cytology is dangerous, as the results of these tests are often misleading and one may miss the opportunity to resect an early cancer. Therefore, the preoperative and, often, operative diagnosis are based mainly on the history and radiologic appearance of the tumors.

Beyond diagnosis, the radiologic evaluation is aimed at determining resectability, as surgical resection is the most effective and only potentially curative therapy. Imaging may locate occult distant metastases and thereby spare patients from nontherapeutic surgery. In defining the degree of invasion of adjacent organs and vasculature, imaging is also essential for planning the surgical procedure and directing major vascular reconstructions when necessary. USG is usually the first investigation performed because it is readily available, and provides important diagnostic information regarding the jaundiced patient.

Generally, intrahepatic biliary dilatation will be seen without evidence of extra hepatic bile duct abnormality and without evidence of stones. In experienced hands, the tumor will often be clearly defined by US, as will

information important for planning of surgery such as delineation of the biliary extent of disease, vascular involvement, presence of lymph node metastases in the porta hepatis, and presence of noncontiguous liver metastases. USG not only may demonstrate the level of biliary ductal obstruction but can also provide information regarding tumor extension within the bile duct and in the periductal tissues. In centers specializing in treatment of cholangiocarcinomas, a good Doppler USG may indeed provide diagnostic information equivalent to that provided by a combination of angiography and CT and is highly accurate in predicting resectability. CT remains an important study for evaluating patients. Important information regarding level of biliary obstruction, vascular involvement, and presence of nodal or noncontiguous metastases can be assessed. One of the most important findings to be gleaned from a CT scan, however, is the presence of hepatic lobar atrophy, which is usually indicative of portal venous occlusion. Recently, however, MRCP has emerged as a noninvasive substitute for direct cholangiography. MRCP not only may identify the tumor and the level of biliary obstruction but also may reveal obstructed and isolated ducts not appreciated at endoscopic or percutaneous study.

For patients presenting with proximal cholangiocarcinomas, a Doppler USG, helical CT, and chest radiograph may suffice as preoperative radiologic evaluation. In patients in whom further delineation of biliary or vascular involvement may be necessary, MRCP and MRA are the next tests of choice. This noninvasive approach prevents biliary instrumentation and bacteremia and the associated increased perioperative

morbidity.

### **Biliary drainage**

The important concept in the prevention of biliary sepsis is the understanding that jaundice alone is not necessarily an indication for biliary decompression. Unlike biliary obstruction in the lower bile duct, where a single stent usually effectively relieves the biliary obstruction, biliary obstruction near the hilus is much more difficult to relieve. Even with a small tumor, a single stent likely will drain only one-half of the liver. When the tumors are large and involve second- or third-order bile ducts, many stents may be required to provide effective biliary decompression; it is also possible that effective biliary decompression cannot be achieved in such cases.

Biliary drainage can be accomplished nonsurgically or surgically. Nonsurgical drainage is preferred if the patient has significant comorbid conditions or if the tumor as evaluated by preoperative imaging is clearly not resectable for cure. Though biliary decompression can theoretically be accomplished either by percutaneous transhepatic puncture or by endoscopic stent placement, hilar tumors are notoriously difficult to traverse with the endoscopic technique.

Moreover, the failure rates and incidence of subsequent cholangitis are high. Thus, most patients with unresectable hilar tumors are not candidates for endoscopic biliary drainage. Percutaneous transhepatic biliary drainage and subsequent placement of a self-expandable metallic endoprosthesis (Wallstent, Cook Medical Devices India Ltd.) is the palliative procedure of choice for these patients.

## Gallbladder cancer

Gallbladder cancer affects women two to six times more often than it does men. The incidence steadily increases with age; reaching its maximum in the seventh decade of life. Seventy-five to ninety-eight percent of all patients with carcinoma of the gallbladder have cholelithiasis.

Gallbladder cancer is usually associated with cholesterol-type gallstones. Other risk factors include the presence of an anomalous pancreaticobiliary duct junction, chronic typhoid infection, and inflammatory bowel disease.

Calcification of the gallbladder (porcelain gallbladder), signifying long-standing inflammation, is associated with gallbladder cancer in 10% to 25% of cases. These conditions suggest that chronic inflammation may play an important role in the development of gallbladder cancer. Though reports of family clusters of gallbladder cancer exist in the literature, congenital predisposition is not believed to play a major role in the development of this cancer.

### Radiologic evaluation

Before the routine use of CT and USG, the preoperative diagnosis rate for gallbladder carcinoma was generally less than 10%, which, in part, explains the dismal outcomes of surgical therapy in the era prior to sophisticated cross-sectional imaging, as many patients with incurable disease were subjected to exploration. With the routine use of CT scanning and real-time US in the 1980s; preoperative diagnosis was achieved in 75% to 88% of patients. Beyond diagnosis, the goals of imaging also include accurate staging. The goal of imaging is to determine extent of liver invasion, invasion of other adjacent organs, vascular involvement, extent of

biliary involvement, presence of nodal metastases, and presence of peritoneal metastases.

Because the majority of patients will present with symptoms suggestive of biliary colic or chronic cholecystitis, the diagnostic workup will usually begin with abdominal USG. Discontinuous gallbladder mucosa, echogenic mucosa, submucosal echolucency, or a mass greater than 1 cm should arouse suspicion of gallbladder cancer. The finding most convincing of a gallbladder malignancy is an inhomogeneous mass replacing all or part of the gallbladder. The index of suspicion should be high for elderly patients, patients with atypical symptoms, and patients with suspicious laboratory findings such as anemia, hypoalbuminemia, and abnormal liver function tests. USG can also delineate the degree of biliary involvement and can define the presence of arterial or portal venous involvement by tumor. In experienced hands, USG will provide diagnostic information equivalent to that provided by much more expensive cross-sectional imaging.

CT scanning is usually the next imaging examination performed because of its wide availability, low cost, low risk, and high yield. On CT, gallbladder cancer can appear as a mass almost filling the gallbladder lumen in 42% of cases, a polypoid mass in 26%, and diffuse wall thickening in 6% of gallbladder cancer patients. CT is better than USG in demonstrating liver atrophy, which usually is indicative of ipsilateral portal vein involvement by tumor. CT is also better at detecting lymphadenopathy, particularly for retropancreatic nodal disease, which would rule out the potential for cure, though CT scan identified only 38% of pathologically positive nodes preoperatively.

Angiography was another common test for assessing vascular invasion when the mass encroached on the porta hepatis, but this invasive method of examination carries finite risks. Cholangiography and angiography remain important tests in certain settings, but Doppler USG, magnetic resonance Cholangiography, and MRA have largely replaced these invasive procedures in the majority of cases.

Magnetic resonance procedures have long been accepted as invaluable for characterizing hepatic tumors. Such procedures may also identify and characterize lymph node metastases with greater precision than can other cross-sectional imaging techniques. With recent advances in hardware and software, the extent of biliary involvement can now be determined through MRCP. MRA allows for assessment of vascular invasion to determine resectability and can demonstrate anomalous anatomic findings to assist in surgical planning.

### Conclusion

Imaging allows early detecting of the tumor in the background of an effective screening procedure and allows identification at a treatable stage. In large tumors > 10 cm in size or diffuse carries a very poor prognosis at the time of detection with a survival of less than 1-year period. Preventive methods are most essential as they are supposed to reduce, the incidence of hepatocellular carcinoma. Once tumor is formed screening procedures has its own limitation and is not 100% effective but screening is well adapted and standard in the west where the persons are screened every 6 months with AFP plus multislice, multiphase CT and abdominal high resolution ultrasound in the hope of early detection and improving survival.

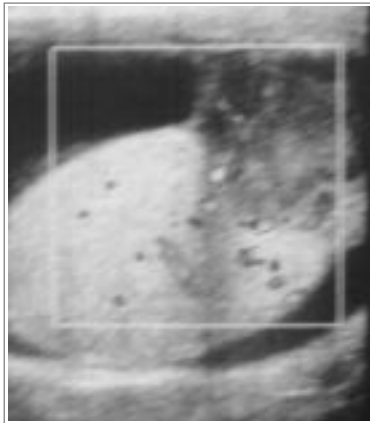
## Case Report of Embryonic Cell Carcinoma Testis

A 54 years old male came to surgery department with complaint of heaviness in right testis and history of minor trauma. On examination, scrotal skin was normal. However right testicle showed a distinct small lump on superomedial aspect. Scrotal USG was done using 7.5 Mhz linear transducer. Right testis showed a distinct hypoechoic mass lesion with few cystic areas and no evidence of any calcification on superomedial side. Doppler USG revealed increased vascularity. Histopathology proved mass lesion as Embryonal cell carcinoma testis (ECCT). There was no evidence of lymphadenopathy on transabdominal USG. Chest radiograph of the patient was normal. So the patient was staged as stage I non-seminomatous germ cell tumor (NSGCT) testis according to Royal Marsden Staging System for testicular cancer. Patient was subsequently treated by right sided orchidectomy.

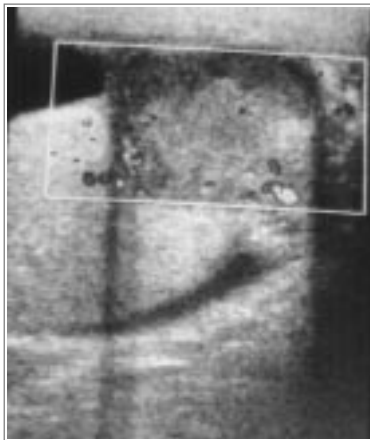
### Discussion

Testicular neoplasms account for 1% to 2% of all malignant neoplasms in men and are the fifth most frequent cause of death in men aged 15 to 34 years<sup>1</sup>. Approximately 65% to 94% of patients with testicular neoplasms present with unilateral testicular masses or diffuse testicular enlargement, and 4% to 14% present with symptoms of metastatic

disease<sup>2</sup>. Most primary testicular tumors are of germ cell origin and are generally highly malignant. Only 60% of testicular germ cell tumors are of one histologic subtype, and the remainder are of two or



Doppler USG Scrotum showing a well defined, hypoechoic mass lesion (containing few cystic areas) with increased vascularity and no evidence of any calcification on superomedial side of right testis. Histopathology report revealed Embryonal cell carcinoma testis.



more histologic subtypes. Although there are potentially several histologic subtypes of germ cell tumor, clinically it is important to recognize only two basic tumor types: seminomas and NSGCT. This is because seminomas and NSGCT behave differently biologically and therefore, have different therapeutic and prognostic implications. Pure ECCT is a rare tumor accounting for only 2% to 3% of testicular germ cell neoplasms. It often occurs in combination with other neoplastic germ cell elements, particularly yolk sac tumors and teratoma. Like other NSGCT, these tumors occur in younger age group than do seminomas, with a peak incidence during the latter part of the second and third decade<sup>3</sup>. The typical ECCT is less homogeneous and well defined while teratomas are heterogenous and more likely than seminomas to contain cystic spaces and calcifications. Seventy percent of stage I NSGCT patients are cured by orchidectomy alone: 30% however will demonstrate subsequent metastatic disease. This can be almost entirely prevented by retroperitoneal lymph node dissection at the time of staging. Alternatively, close radiological surveillance can be instituted to allow early detection of metastatic disease with chemotherapy.

Around 25% of NSGCT patients have metastasis (Stage II-IV) at presentation and these are also treated with chemotherapy which is usually associated with complete response. Around 25% however will demonstrate persistent



lymph node mass following chemotherapy. No imaging modality is currently completely reliable in determining which masses contain significant disease and generally these are treated with surgical excision (retroperitoneal lymph node dissection) <sup>4</sup>.

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## Case Report of Multicystic Dysplastic Kidney with Pregnancy

A 26 years old primigravida with no history of any illness or drug intake during pregnancy came for routine obstretic ultrasound. Sonography demonstrated a single live intrauterine pregnancy of about 33 weeks

gestation age. Placenta was in the anterior and superior segment. Fetal head was enlarged with dilated bilateral side lateral ventricles (atria measured approx 26 mm). Fetal right side kidney appeared enlarged and showed non-communicating cysts of variable sizes along with nonvisualised normal renal parenchyma. Fetal left side kidney and urinary bladder appeared normal. Liquor amnii was normal. USG findings were suggestive of right side multicystic dysplastic kidney (MCDK) with hydrocephalus. Patient underwent caesarian section and findings were confirmed.

### Discussion

Unilateral MCDK is the second most common urinary tract abnormality diagnosed antenatally. Simple MCDK is defined as unilateral renal dysplasia without additional genitourinary (GU) abnormalities. Complex MCDK includes patients with bilateral renal dysplasia or unilateral renal dysplasia with other GU abnormalities. The final outcome for patients with simple MCDK is quite good, with normal renal function and compensatory hypertrophy of the contralateral kidney in all patients. In contrast, patients with bilateral disease or associated GU anomalies have a higher incidence of UTI and progression to renal failure <sup>1</sup>. Patients with antenatally or neonatally detected multicystic dysplastic kidney can primarily be followed up conservatively. Involution occurs in approximately one fourth of the cases, usually within about 14 months. No significant involution can be expected to occur after 18 months. If surgery is decided on, we recommend an age of about 2 years. Late complications (e.g., Wilm's tumor and renovascular hypertension) are rare <sup>2</sup>. The term ventriculomegaly (VM) describes large



1. USG Skull showing bilateral dilated lateral ventricles with thin cortical parenchyma suggestive of hydrocephalus.
2. USG abdomen showing right kidney replaced by non-communicating cysts of variable sizes suggestive of multicystic dysplastic kidney.



3. USG Skull and USG Abdomen showing right multicystic dysplastic kidney with hydrocephalus.



ventricles. Hydrocephalus (HC) refers to enlarged ventricles associated with increased intracranial pressure and / or head enlargement. VM is the most common cranial abnormality. The atrium of the lateral ventricle is the site of confluence of the bodies, occipital horns, and temporal horns. Cordoza reports that between 14 and 38 menstrual weeks, the transverse atrial measurement is constant at 7.6 mm (standard deviation 0.6 mm). Measurement above 10 mm suggests VM with a low false-positive rate. Borderline VM indicates measurements 10 to 15 mm, and marked VM indicates measurements above 15 mm<sup>3</sup>.

Once enlarged ventricles are discovered, it is important to search for the etiology and any associated abnormalities because they determine the prognosis. Actual ventricle size is less prognostic<sup>4</sup>. VM generally stays stable or increases slightly (about 85%) but a small proportion may resolve and become normal (about 15%). Aneuploidy is found in about 3% to 12.6% of all VM fetuses and 4% with isolated VM, most commonly trisomy 21 and trisomy 18.

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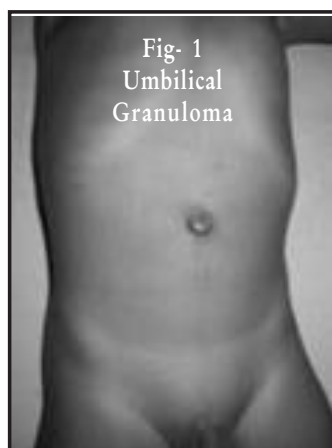
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## Vitelline Duct Anomaly - a Case Report

**V**itelline duct is a remnant of yolk stalk which connects yolk sac to the midgut in developing embryo<sup>1</sup>. A number of anomalies are found to be associated with its partial or complete persistence. Herewith, we present a rare case of complete



persistence of Vitelline duct (Meckel's diverticulum) which was connecting ileum to the umbilicus.

3 yrs old male child was presented with H/o reddish discolouration and



Fig- 2  
On  
ultrasound  
examination  
of the  
abdomen,  
there was  
hypo

intermittent mucoid discharge through the umbilicus since birth. There was no history of faecal discharge. On clinical examination a chestnut size tumour was seen at the umbilicus, discharging mucoid secretions. (Fig.1) Diagnosis of umbilical granuloma with Vitelline duct anomaly was made.

On ultrasound examination of the abdomen, there was hypoechoic tubular structure with central hyperechoic line having the gut signature<sup>2</sup> with 'L' shape, seen connecting the umbilicus to the small bowel. The vertical limb was measuring 2 cms and horizontal segment was measuring 5 cms. Colour Doppler showed increased vascularity in the hypoechoic muscular portion. No associated kidney or urinary bladder anomalies were seen.

Sinogram using water soluble contrast (Angiograffin 65%) was done with 8F cannula. Contrast was injected with gentle pressure. Contrast was seen going into the tract through the umbilicus, although intestinal communication was not demonstrated, faint visualization of the intestine was seen.

Patient's CBC, renal function tests and urine examination were normal.

Patient was operated upon. There was a long tubular structure seen connecting the umbilicus to the ileum. The lumen

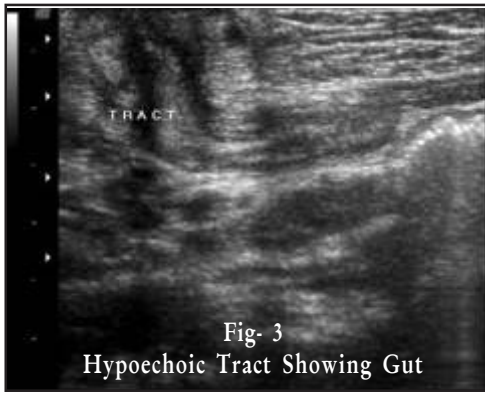


Fig- 3  
Hypoechoic Tract Showing Gut

proximal to ileocaecal junction. Different types of anomalies may be seen with the partial or complete persistence of Vitelline duct<sup>3</sup>. There can be a sinus tract or fistula or atretic tract. Complications include diverticulitis, bleeding, ulceration, perforation,

can be a good diagnostic tool to know the anatomical details. Surgery can be planned accordingly.

Radionuclide imaging with <sup>99</sup>Tc pertechnetate shows increased uptake, if there is presence of ectopic gastric or pancreatic tissue<sup>1</sup>.

Angiography will show extravasations of contrast medium into diverticulum in case, there is active bleeding.

Thus imaging study specially USG and contrast study can play a vital role in diagnosis and surgery can be planned or modified accordingly.

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was patent. The site of the diverticulum was proximal to the ileo-caecal junction on antimesenteric border of the ileum. Catheter could be negotiated into the diverticulum through the umbilicus. It went down into the lumen of the intestine. The tract was clamped at the base after dividing the mesentery. The diverticulum was resected with the umbilical granuloma in continuity. The rent in the small bowel was repaired. Abdominal wall was sutured in layers. There was no other anomaly found.

Histopath examination showed a fibrous tract lined by stratified squamous epithelium alongwith intestinal mucosa. Mucosa showed finger like villi with dysplastic epithelium with intact basement membrane. Findings suggestive of Meckel's diverticulitis with organized granuloma at the umbilicus. There was no evidence of ectopic gastric or pancreatic tissue seen in the Meckel's diverticulum.

### Discussion

Meckel's diverticulum has an incidence of 2% and is formed by persistence of Vitelline duct which arises from 1-2 feet

intestinal obstruction, volvulus or gangrene<sup>1</sup>.

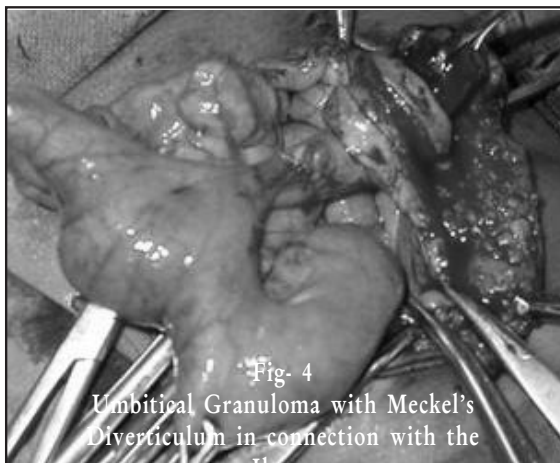


Fig- 4  
Umbilical Granuloma with Meckel's Diverticulum in connection with the

Radiologically small bowel enema or Barium meal follow through can demonstrate blind ending sac arising from antimesenteric border of ileum<sup>4</sup>. Sometimes a triradiate pattern of mucosal folds is seen at the base<sup>1</sup>. When it is inverted, a filling defect is seen similar to polyp. The method is cumbersome and not very informative.

USG shows hypoechoic tubular structure with a gut signature which can mimick appendicitis. This

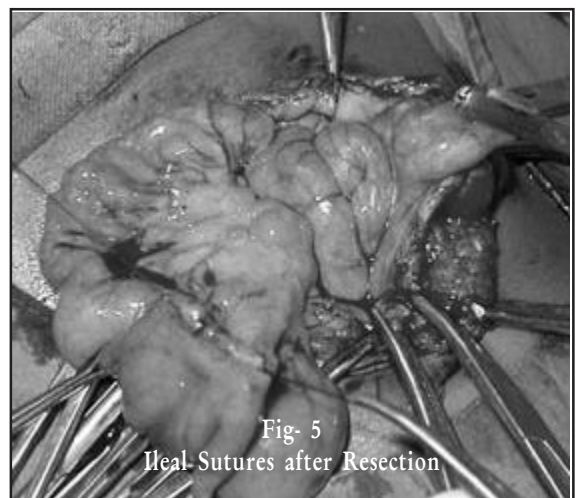


Fig- 5  
Ileal Sutures after Resection

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## Case Report of Scrotal Calculus

A 75 year old male came to surgery department with history of fever for five days and complaint of pain lower abdomen alongwith inability to extend left hip. USG abdomen using 3.5 Mhz sector transducer was found to be normal. Further USG of bilateral inguinal and scrotal region was done using 7.5 Mhz linear transducer. Testes and epididymis of both sides showed normal size and echotexture. Right sided scrotal sac revealed fluid with thick internal echoes suggestive of right side pyocoele. Left side scrotal sac revealed fluid with no internal echoes. A 11 mm mobile echogenic focus with distal acoustic shadowing was also seen in left side scrotal sac. Findings were suggestive of left side scrotal calculus alongwith left sided hydrocoele.

## Discussion

Scrotal calculus, also known as fibrinoid loose body or scrotal pearl, is a benign nonneoplastic extratesticular mass, first described by Kickham in 1935<sup>1</sup>. The calcified loose body arises from the tunica vaginalis and may break free to become a loose body between the two membranes of the tunica vaginalis testes.

Grossly, these calculi appear as round, pearly white, rubbery masses. Histologically, scrotal pearls are composed of a central nidus of hydroxyapatite around which fibrinoid material is deposited. Thought from hematomas, or from inflammation of the tunica vaginalis testes, these calcifications may present as either painful or nontender free floating or dependent scrotal masses<sup>2</sup>. Because of their association with inflammatory scrotal processes, hydrocoele is a common secondary finding. The presence of a hydrocoele may make the calculus more conspicuous and conversely, the absence of an associated hydrocoele may render identification of a calculus more challenging<sup>1,2</sup>. The presence of calculus in a hydrocoele does not change the prognosis or treatment of this condition, although some doubts may arise during sonographic assessment if it is attached to the parietal portion of the tunica vaginalis<sup>3</sup>.

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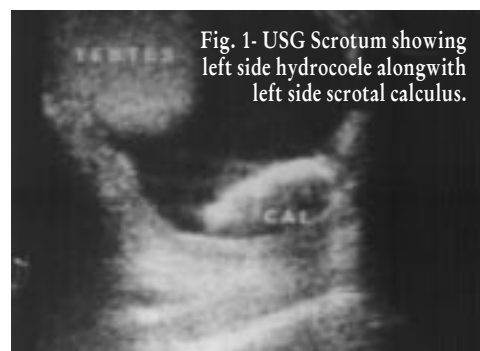


Fig. 1- USG Scrotum showing left side hydrocoele alongwith left side scrotal calculus.

Fig. 2  
USG Scrotum showing scrotal calculus in relation to left testis.



## Case Report of Gall Bladder Polyp

A 33 years old male presented with complaint of pain in right hypochondrium. On trans-abdominal USG, gallbladder was distended and showed multiple echogenic foci (of sizes varying from 5 to 9 mm) with no posterior acoustic shadowing, protruding from the wall of the gallbladder into the gallbladder lumen. Thus the imaging findings revealed the diagnosis of gallbladder polyps. Patient was advised cholecystectomy for

symptomatic gallbladder polyps. Patient refused surgical treatment and was managed conservatively.

### Discussion

Gallbladder polyps affect approximately 5% of the adult population<sup>1</sup>. Polypoid lesions of the gallbladder (PLG) include benign pseudotumors (cholesterol polyps, adenomyomatosis), benign (adenoma) and malignant (adenocarcinoma) neoplasms. Cholesterol polyps are the most common PLG and are usually less than 10 mm in size. Cholesterol polyps have a characteristic pedunculated appearance on USG and are often multiple (30% of cases).

Adenomyomatosis appears as a sessile polyp with characteristic microcysts on USG and is most often larger than 10 mm. Adenoma and adenocarcinoma may be sessile or pedunculated and are usually larger than 10 mm. In the absence of transmural invasion, it is difficult to differentiate sonographically between adenoma and adenocarcinoma<sup>2</sup>. B-ultrasonography is the most effective diagnostic method for detecting PLG<sup>3</sup>. Endoscopic USG may be more sensitive and specific than transabdominal USG in differentiating among PLGs.

Endoscopic USG and positron emission tomography may prove to be useful in assessing the malignant potential of large gallbladder polyps. Most small PLG are benign and remain static for years. Age more than 50 years and size of polyp more than 10 mm are the two most important factors predicting malignancy in polypoid lesions of the gallbladder. Other risk

factors include concurrent gallstones, solitary polyp, and symptomatic polyp<sup>4</sup>. Patients who have biliary pain and small gallbladder polyps without gallstones present a difficult management decision for the clinician. If the clinician is confident that the polyps are the source of the pain, patient should be referred for cholecystectomy. Laparoscopic cholecystectomy is the treatment of choice unless the suspicion of malignancy is high, in which case it is advisable to have open exploration, intraoperative frozen section, and preparation for extended resection<sup>4</sup>.

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Fig 1

Echogenic lesions with thin stalk and no posterior acoustic shadowing distending into gallbladder lumen from non-dependent gallbladder wall suggestive of gallbladder polyps.



Fig 2

## Case Report of Splenic Hydatidosis

A 38 year old female presented to surgery department with complaint of pain in left hypochondrium. X Ray abdomen revealed diffuse soft tissue haze in left hypochondrium displacing the splenic flexure of colon inferiorly. USG abdomen revealed a single, well defined, multicystic mass in spleen suggestive of hydatid cyst with multiple daughter cysts. Contrast enhanced CT abdomen revealed a well defined, single hydatid cyst with multiple daughter cysts in spleen. So final diagnosis of splenic hydatidosis was made and patient was advised surgery. Patient underwent splenectomy thereafter and is doing well on follow up.

### Discussion

Hydatid disease commonly affects liver and lungs. Incidence of extra-hepatic hydatid varies from 14% to 19%<sup>1,2</sup>. Splenic hydatidosis is rarely encountered in clinical practice occurring in 1.5%-4% of patients with echinococcus granulosus infestation<sup>3</sup>. Primary splenic hydatidosis develops when the parasite escapes to the hepatic and pulmonary filters whereas secondary disease is related to ruptured intra-abdominal cysts. Intra-abdominal rupture is a typical complication of splenic hydatidosis.

Hydatid cyst consists of three layers:

- an adventitia formed of compressed host tissue
- a middle layer of friable ectocyst
- an inner germinal layer from which is produced large number of scolices which are the heads of developing worms.

The diagnosis of uncomplicated hydatid

cyst depends on high index of suspicion. Various biochemical, serological and imaging techniques can be used. The casoni's test has poor sensitivity and a high rate of false positives. ELISA is positive in more than 90%. Though the risk of parasite diffusion is high, FNAC can greatly increase the chance of definitive diagnosis of hydatidosis by finding protoscolices or antigen 5.

USG is a sensitive and cost-effective imaging technique. USG is helpful in defining the internal structures, number and location of the cysts and complications. The specificity is around 90%. CT yields better information about the location, number and presence of daughter cysts. Splenectomy remains the therapeutic procedure of choice for splenic hydatidosis. Hypertonic saline solution is widely used in surgery for intra-abdominal or intra-thoracic echinococcosis for its supposed antiparasitic action<sup>3</sup>.

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Approximately 75000 new cases of breast cancer are estimated to occur in Indian women every year. The breast cancer is the second most common cancer after cervix uteri<sup>1</sup>. Increasing awareness, promotion of self-palpation, increasing use of mammographic and imaging techniques are bringing out more and more patients with palpable and non-palpable lesions to medical attention. Mammography, ultrasonography and contrast enhancing nuclear magnetic resonance have been useful tools in clinical evaluation<sup>2</sup>. Application of microarray technology for evaluation of expression of thousands of genes may isolate, in future, the women with high risk for developing carcinoma of breast. Even then, till date, the management of breast lesion remains largely dependent on critical microscopic examination of tissue / cells obtained from the lesion.

### Techniques

**Aspiration vs surgical biopsies, frozen section, sentinel lymph node-**Techniques for pathological evaluation include Fine Needle Aspiration Cytology (FNAC), Needle Core Biopsy (NCB), Stereotactic Core Biopsy and Frozen Section. The advent of FNAC has brought down a decrease in the number of open biopsies. The harvest of tumor cells obtained provides a cost effective assessment of morphology and can be subjected to immunohistochemistry, hormone studies, cell kinetics and DNA analysis<sup>3</sup>. Cell blocks can be prepared by

collecting aspirated material in 5 ml of 50% ethanol / 10% formalin, and centrifuged deposits or cell pallets after filtration are subjected to routine tissue processing.

Cytology of nipple discharge and scrape preparation from nipple and skin lesions are non-invasive tools providing useful information in mastitis and intraductal papillary lesion. Since needle core biopsy (NCB) provides information about architectural pattern, they are generally preferred over FNAC. In non-palpable and gray zone diagnoses of breast lesions [like Phyllodes tumor, Lobular carcinoma, Ductal Carcinoma In Situ (DCIS)], a definitive diagnosis is rendered in over 90% of cases by NCB<sup>5</sup>. Stereotactic core biopsy is a reliable alternative to excision biopsy in diagnosis of non-palpable suspicious lesions or microcalcifications detected on mammography. Two X-ray images of breast lesions are taken at different angles. A computer uses the images to locate the abnormality and calculate precise coordinates to guide the physician in placing a needle at the target. Studies have revealed 96% concordance between stereotactic core biopsy and excision biopsy for the invasive and in situ cancer and 78% concordance for type of cancer. Excision biopsy has to be performed if the lesion is diagnosed Atypical Ductal Hyperplasia (ADH) to rule out DCIS and if the pathology findings do not correlate with mammography<sup>6,7</sup>.

Frozen section is still useful in evaluating re- excision lumpectomy margins. It

should not be attempted in lesions less than 1.0 cm, papillary lesions and non-palpable lesions screened positive for microcalcification on mammography. Although highly accurate with false positivity rate of zero and false negative rate less than 1%, the technique has been largely substituted by pre operative needle aspirations and biopsies except for assessment of margins and intra operative assessment of sentinel lymph node<sup>8</sup>.

The sentinel lymph nodes are identified by the surgeon during operative procedure, after injecting dye or radiolabelled tracer material. If negative on frozen section, the lymph node is step sectioned at three levels on paraffin embedding, to be stained with haematoxylin and eosin (H&E) and at least one section immunostained for Keratin cocktail (AE1/AE3)<sup>9</sup>. Presence of single cells is reported as isolated tumor cell metastasis and cluster of cells not more than 2 mm as micro metastasis. Other keratin positive cells including reticulum cells, mesothelial cell inclusions, ectopic breast tissue and traumatic displacement of breast epithelium induced by biopsy procedure result in false positivity. If sentinel node is negative, it is presumed that the other nodes of group will be negative. There are one-third chances of other nodes being positive if sentinel lymph node is positive<sup>10</sup>.

A basic surgical pathology report on a mastectomy specimen should include diagnosis with histological type and grade – nuclear grade, tubule formation,

mitotic count and composite histologic grade; maximum diameter of invasive tumor, site and extent of in-situ component if present, vascular invasion, margins, nipple and any other significant features. Report of lymphnodes should be formulated informing total number of nodes, involved nodes (number) and deposits more than 2 cm (macrometastasis), extracapsular invasion and tumor emboli in perinodal lymphatics. Many laboratories are now routinely reporting steroid hormone receptors status and HER-2 / neu (c-erb B-2) expression in tumors<sup>11</sup>.

### Diagnostic gray zone

**(Inflammatory lesions, hyperplasias vs atypical proliferative lesions vs in situ carcinomas)**

### FNAC

Overdiagnosis of cancer on FNAC may occur in fibroadenoma, fibrocystic disease with florid or atypical ductal hyperplasia, fat necrosis with reparative inflammatory atypia and lactation adenoma. Although presence of myoepithelial cells, bipolar bare nuclei and stromal fragments favor benign pathology; the high cellularity and nuclear atypia may be misleading<sup>12</sup>. Papillary lesions are difficult ones on aspiration and nipple discharge cytology in the absence of obvious malignant features and are reported as papillary lesions requiring histopathology for further categorization (papillary hyperplasia, papilloma and papillary carcinoma). Irregular and palisaded arrangement, tall columnar single cells, nuclear moulding and mitotic figures in the absence of myoepithelial cells favor malignancy<sup>13</sup>. Helpful clues in differentiating phyllodes tumor of borderline and low-grade malignancy

from fibroadenoma are hypercellular stromal fragments with mitotic activity in the aspiration cytology smears<sup>14</sup>. Low cellularity with minimal cytological atypia may result in false negativity in low grade DCIS, lobular carcinoma and tubular carcinoma. Experience and acumen of cytopathologist are of utmost importance in such cases<sup>13</sup>. Some lesions like fat necrosis, chronic granulomatous inflammation, periductal mastitis and lymphocytic mastopathy may be misdiagnosed on clinical assessment, mammography and even on aspiration cytology; generally because of either atypical looking histiocytes or regenerative epithelium and stromal reaction. Variable sized atypical macrophages and histiocytic giant cells in fat necrosis may be misinterpreted by uninitiated. However, background of granular debris, fat and fragments of adipose tissue, chronic inflammatory cells and absence of epithelial cells are helpful features<sup>15</sup>. A cavity developing in few long-standing cases with fibrosis and calcification in the wall has been termed membranous fat necrosis<sup>16</sup>.

### Inflammatory lesions

Chronic granulomatous inflammation in the breast may be observed because of diverse etiology, and at times, it becomes extremely difficult to correctly identify the cause on morphological examination alone. Caseating granulomas, demonstration of acid fast bacilli, highly reactive tuberculin test or serology against mycobacteria, evidence of infection elsewhere in body and PCR establish tuberculous etiology. Interferon  $\gamma$  tests, demonstrating production of  $\gamma$  interferon and quantification of activated T lymphocytes obtained from the patient and challenged with Early Secretory Target (ESAT)-6 and Culture Filter

Protein (CFP)-10, are supposed to be specific for tuberculosis and differentiate it from non tuberculous mycobacteria and BCG induced positive serology<sup>17</sup>.

Naked or healing granulomas, with or without presence of Schaumann or Asteroid bodies, but without caseation, increased serum levels of angiotensin converting enzyme (ACE), calcium and negative tuberculin test suggest possibility of sarcoidosis. Biopsy from asymptomatic gastronemius muscle may be a helpful clue. Suppurative granulomas may be observed in atypical mycobacteriosis as well as in fungal infections; to be differentiated by demonstration of microorganism on acid fast staining, Periodic Acid Schiff reaction, silver methanamine and appropriate culture<sup>18</sup>.

If all causes have been excluded, necrotizing suppurative granulomas, sometimes with formation of abscess and even sinuses, mostly confined to lobules, may be because of idiopathic chronic granulomatous mastitis, also termed as *Perilobular Mastitis*. Autoimmune etiopathogenesis appears to be the mechanism, and early recognition and initiation of steroid hormone, results in complete remission of the disease<sup>19</sup>. Nipple retraction and discharge may mimic carcinoma in periductal mastitis (Duct Ectasia). Smears from nipple discharge mostly reveal macrophages with few benign epithelial cells<sup>20</sup>. Dense fibrosis, lobular atrophy, lymphocytic infiltration in perivascular and perilobular distribution on biopsy from Painful palpable or non palpable mass in young to middle aged women, often in association with Type 1 diabetes are diagnostic of lymphocytic mastopathy / lymphocytic lobulitis. Prominent atypical change in stromal cells with granular cytoplasm observed



in the lesion should not be confused with granulomatous inflammation and carcinoma, as most of these lesions eventually show resolution of inflammation<sup>21</sup>. The most common complications reported after silicon implants include; capsular contraction, an exaggerated and normal response to foreign material: which microscopically is seen as increase in dense collagen, synovium like metaplasia of wall, foreign body reaction around the implant. Silicon gel leakage may produce oval cystic spaces sometimes filled with amorphous but non birefringent material. The foreign body reaction may mimic malignancy clinically and on histopathology<sup>22</sup>.

### Proliferative lesions

Morphological assessment may be difficult in differentiating some benign lesions from malignant ones such as Sclerosing Adenosis, Radical Scar / Complex Sclerosing Lesion (RS / CSL), Microglandular Adenosis (MGA) from tubular carcinoma and their differentiation from each other, both on aspiration cytology and needle biopsy<sup>23-26</sup>. Low power magnification observations are of extreme importance in identifying and differentiating RS/CSL, sclerosing adenosis, microglandular adenosis and tubular carcinoma from each other. Radical scars / complex sclerosing lesions are distinctive stellate lesions characterized by scleroelastotic center having a glandular distribution and over all appearance like the head of flower on low power magnification. The lesions measuring 1-9 mm are designated radical scar and those, which are 10 mm, or more should be termed complex sclerosing lesion<sup>25</sup>. In sclerosing adenosis, there is a numeric increase in glandular elements accompanied by stromal proliferation, which produces glandular compression

and distortion. Low power examination reveals multiple nodular areas with retention of over all lobular architecture. Microglandular adenosis is rare benign lesion with proliferation of small ductular or acinar structure in which rule of two cells type is broken<sup>23,24</sup>.

Preservation of myoepithelial cell layer in flattened ducts, entrapped in dense relatively acellular stroma, is observed in radial scar. Disordered proliferation of microtubules lined by epithelial and myoepithelial cells [the latter at times extremely difficult to perceive and may require identification by immunostaining for anti Smooth Muscle Actin(SMA)], arranged in lobulocentric configuration, supports diagnosis of sclerosing adenosis<sup>23</sup>. Myoepithelial cells are missing from tubules of microglandular adenosis and tubular carcinoma. Rounded glands, at places lined by multilayered epithelium along with PAS positive secretion in the lumen and abnormally distributed in mammary stroma and fat are diagnostic of MGA. The glandular structure in tubular carcinoma is angulated with branching in some, and is lined by large cells with abundant eosinophilic cytoplasm and apical snouts. The stroma is desmoplastic with variable fibrosis and elastosis and shows characteristic metachromasia<sup>24,25</sup>.

Diagnosing and typing of in-situ carcinoma (DCIS) and differentiating it from Atypical Ductal Hyperplasia (ADH) on one hand and invasive carcinoma on the other may be troublesome. It may require extensive sampling and sectioning as well as competence of the pathologist. Interpretation of papillary lesions also falls in gray zone even on histopathology. Whereas presence of mixed cell population of ductal epithelial and myoepithelial cells growing in streaming

and flip flap fashion, arrangement in three dimensional sheets revealing slit like fenestrated, irregular and interconnected spaces favor ADH, single cell population with out spindle cell component, nuclei oriented towards the lumen and punched out sieve like spaces are the features suggestive of cribriform DCIS<sup>27</sup>. Variable distention of Terminal Duct Lobular Unit (TDLU) by proliferating acinar cells on lower magnification is observed in lobular hyperplasia, as well as in lobular carcinoma, with overlapping features described in Atypical Lobular Hyperplasia (ALH) vs. in-situ Lobular Carcinoma (LCIS). Lobular hyperplasia is called atypical when less monotonous, variable sized, cohesive cells incompletely fill the TDLU with somewhat irregular spaces. In LCIS, there is greater distension of acini compared to ALH, the cells are monotonous but less cohesive and fill the TDLU completely<sup>28</sup>. DCIS is differentiated from LCIS with the presence of cohesive cell groups without intracytoplasmic lumina, and with variable nuclear and cytoplasmic atypia arranged in variable sized glands, rosettes, papillae or solid areas in the former and poorly cohesive, monotonous evenly distributed cells with intracytoplasmic mucin, high nuclearcytoplasmic ratio, hyperchromatic nuclei with inconspicuous nuclei, completely filling the acini in later<sup>29</sup>. All forms of DCIS can extend to involve the acinar units of TDLU. Similar morphological appearance of the cells in acini and duct spaces differentiate if from LCIS and ALH, which are lobulocentric and extend in the ducts in a pagetoid fashion. Lobular neoplasm has discohesive cells due to loss of E-cadherin (specific marker for lobular epithelial lesions of breast)<sup>30,31</sup>.

Presence of fibrovascular core covered by epithelium distinguishes papillary neoplasm from papillomatosis. Papilloma may not be differentiated from papillary carcinoma on frozen section. A well-developed fibrovascular core lined by epithelial cells revealing benign nuclei and mixed with myoepithelial cells, with or without presence of apocrine cells, indicates benign tumor. Poorly developed or delicate fibrovascular core, absence of myoepithelial cells, epithelial cells with atypical nuclei lined perpendicular to central core and sheets of variable thickness favour papillary carcinoma<sup>32</sup>.

### Uncommon carcinomas

Malignancies other than adenocarcinomas (squamous cell carcinoma, phyllodes tumor, sarcoma and lymphoma) make up fewer than 5% of all the breast malignancies. In-situ carcinoma and invasive carcinoma are differentiated on the basis of malignant cells crossing the basement membrane into the stroma in later with a potential to invade the vasculature and metastasize into regional lymph nodes and distant sites. In-situ carcinomas, however, can extend to the overlying skin through the ductal system as Paget's disease. Although morphologically classified as ductal or lobular on the basis of resemblance to these structures, all carcinomas are thought to arise from TDLU and do not imply a site or cell type of origin. Ductal carcinoma in-situ (DCIS), most often non palpable or vaguely palpable mass (earlier diagnosed as incidental finding in a biopsy for other lesions), are being detected with increasing frequency on mammographic screening as microcalcification or less often as density. It involves only a single ductal system or spread through out ducts and

lobules involving an entire sector of breast. In contrast to LCIS, these are generally monofocal lesions without skip lesions beyond 10mm and may be treated with complete excision ensuring a clear margin of 10mm<sup>33</sup>.

Historically five architectural subtypes *Comedocarcinoma* (high grade with central necrosis), *Solid* (high grade, completely filling the ducts), *Cribriform* (low to high grade), *Papillary* with fibrovascular core and *Micropapillary* having bulbous protrusions without a fibrovascular core (intermediate grade) have been described. Interestingly, mammographic calcifications are more often-calcified intraluminal secretion than central necrosis. Uncommon variants have been reported<sup>34</sup>. Small cells solid DCIS made up of uniform population of cells extending to TDLU may be indistinguishable from LCIS. Discohesion of cells favours later. Apocrine DCIS should be differentiated from apocrine metaplasia and atypical apocrine hyperplasia on the basis of characteristic cytoarchitectural features and extent of lesion occupying the space (discussed in biopsy interpretation). It is further categorized, on the basis of cell cytology, in low grade (non necrotic) and high grade (necrotic) apocrine DCIS<sup>35</sup>. Neuroendocrine DCIS, usually seen in elderly women and presenting with nipple discharge, may be misdiagnosed as benign lesions. Arranged in papillary or solid pattern, the cells are polygonal, oval or spindle with high N/C ratio and granular cytoplasm. Mucin is present in the lumen and cells show negative argentaffin and positive argyrophilic reaction. Clinging pattern refers to scanty tumor cells attached to the duct lining epithelial layer irrespective of nuclear grade. It is possibly not a distinct entity but a variant of ADH, micropapillary

DCIS or large cell DCIS. An interesting variant is cystic hypersecretory DCIS. Cells line the ducts with more abundant cytoplasm revealing a secretory change, forming large distended cystic spaces filled with colloid like material. Signet ring cells DCIS has also been described; though signet ring cell pattern is rather characteristic of LCIS<sup>36,37,38</sup>.

It must be borne in mind that all though there are many histomorphologic marvels giving delight to the histopathologist, pure forms are uncommon and different entities may simply be variants of common forms. Invasive carcinoma may be a firm palpable mass fixed to skin with retraction of nipple, and at times manifest as enlarged erythematous breast due to extensive involvement of dermal lymphatics known as inflammatory carcinoma, mimicking inflammatory conditions on clinical examination, causing delay in diagnosis. Rarely, the primary can be small or obscured by dense breast tissue manifesting as metastasis in axillary nodes and distant sites with occult primary<sup>39</sup>. The common histologic types include Invasive Duct Carcinoma (IDC), No Special Type (NST), lobular carcinoma, tubular, mucinous (colloid), cribriform, medullary and papillary carcinomas<sup>40</sup>. Carcinoma associated with large amount of DCIS requires wide excision to reduce local recurrences.

Lobular carcinoma, in one fourth of the cases, has a diffuse pattern of invasion without prominent desmoplasia; producing only a vaguely thickened area and subtle architectural changes on mammography. Greater incidence of bilaterality of this tumour is being questioned, due to bias for performing contralateral surgery in such patients. Hormone replacement therapy, in post

menopausal patients, may be responsible for increased incidence reported in this age group. Most lobular carcinomas show loss of a region on chromosome 16 (16q.22.1) including a cluster of gene for cell adhesion molecule (E Cadherin and b Catenin). Metastases to peritoneum, retroperitoneum, the leptomeninges, GIT, and the ovaries and uterus are observed more frequently as compared to other carcinomas<sup>30,41</sup>. Although comprising less than 2% of invasive carcinomas, identifying special type of carcinoma is important because in a given clinical context, adjuvant treatment will be spared in tumors with good prognosis and vice versa and aggressive tumor will be treated vigorously. Considered to be of poor prognosis, invasive micropapillary carcinoma is characterized by clusters of cells in micropapillary (apical surfaces of the cells polarized insideout, without a fibrovascular core.) or tubuloalveolar arrangement suspended in a clear space/ mucinous or aqueous fluid mimicking serous papillary carcinoma of the ovary. Vascular or lymphatic invasion may be extensive. Expression of ER/PR, HER2/neu, P53 and bcl2 has been reported in a variable but significant proportion of cases<sup>42,43</sup>.

Histologically identical to its counterpart in salivary glands, adenoid cystic carcinoma is differentiated from cribriform carcinoma by the presence of two cell population of epithelial and myoepithelial cells, alcian blue positive mucin in large and PAS positive granules in small cystic spaces and usually negative staining for hormone receptors<sup>44</sup>. Occasional case reports include; mucoepidermoid carcinoma, clear cell hidradenoma and eccrine spiradenoma (originating in breast away from overlying skin). Pleomorphic adenoma

and syringomatous tumor in the region of nipple have also been reported<sup>41</sup>.

Signet ring cell appearance, in a variable population of cells has been observed in lobular carcinoma (otherwise showing characteristic discohesive monotonous cell population), ductal carcinoma and metastasis. A poor prognostic variant, ductal signet ring cell carcinoma is diagnosed on finding more than 20% of neoplastic cells having discrete mucicarmine positive/ diastase resistant PAS positive vacuoles in contrast to confluent vacuoles pushing the nucleus to one side in metastasis from other organs. Unusual propensity to involve GIT, serosal and submucosal surfaces of bladder and stomach have been reported<sup>45</sup>.

A carcinoma first described in children with a favourable prognosis manifesting as a well defined nodule due to peripheral fibrosis is juvenile / sclerosing carcinoma. The tumor shows a clear cell pattern due to presence of intra and extracellular Alcian blue and diastase labile PAS stain. Similar tumor observed in adult patients carries poor prognosis<sup>46</sup>. A poorly differentiated tumor with nuclear irregularity has been described with cytoplasmic vacuoles of lipids positive with oil -red O<sup>47</sup>. Neuroendocrine differentiation has been described in lobular carcinoma, ductal and mucinous carcinomas. Less than 0.5% of all mammary carcinoma may be composed predominantly, or entirely, of apocrine cells and are referred to as apocrine carcinoma, behaving prognostically like IDC of similar grade<sup>48,49</sup>. Epithelial, myoepithelial tumors are unusual tumors of breast. In adenomyoepitheliomas, nodules of spindly myoepithelial cells resembling smooth muscle cells surround glandular

element. Any one of the components may turn malignant with recurrence and metastasis. Biological behaviour is unpredictable and does not correlate well with histology<sup>50</sup>. Squamous cell carcinoma and heterologous differentiation such as cartilage, bone, myxoid stroma and poorly differentiated spindle cell component in an adenocarcinoma is referred to as metaplastic carcinoma accounting for less than 0.2% of invasive carcinomas. Pleomorphic spindle cell producing appearance of a high-grade sarcoma with poor prognosis is the most common metaplastic element<sup>51</sup>. A tumor, predominantly composed of bipolar spindle cells of relatively bland appearance arranged in interlacing bundles termed as spindle cell carcinoma, may be difficult to differentiate from benign spindle cell proliferation of fibromatosis<sup>52</sup>. Abrupt transition from carcinoma to an osseous or cartilaginous matrix with out zone of transition has been termed as matrix producing carcinoma<sup>53</sup>. Low-grade adenosquamous carcinoma may look like syringomatous tumor of minor salivary gland, microcystic adnexal carcinoma of skin in the region of lip and syringomatous adenoma of nipple. Its association has been reported with sclerosing adenosis, radical scar, ductal adenoma, papilloma and adenomyoepithelioma suggesting probability of all these entities belonging to a broad spectrum of adenomyoepithelial lesions<sup>54</sup>. Pure squamous cell carcinoma of breast is rare, and must be diagnosed only after thorough sampling does not reveal any area of adenocarcinoma. Squamous differentiation is not uncommon in IDC<sup>55</sup>.

## Prognostic factors in breast cancer

Increasing choice of therapeutic modalities is available today for breast carcinoma including surgical excision varying from conservative approach to radical dissection, various types of chemotherapeutic regimes and radiotherapy. Prognostic and predictive factors help in choosing the most appropriate modality. Prognostic factors provide information useful in assessing the outcome at the time of diagnosis whereas predictive factors provide information about likelihood of response to a given therapy. The degree of epithelial proliferation in the breast lesions correlates with the magnitude of risk of developing invasive carcinoma. Patients with no or mild hyperplasia have no increased risk for subsequent invasive carcinoma; whereas moderate or florid hyperplasia increases the risk 1.5 to 2 times. The risk becomes five folds with ADH or ALH and eight to ten fold with DCIS or LCIS<sup>56</sup>.

The prognostic factors can be broadly classified as conventional and molecular. Amongst conventional prognostic factors, age less than 50 years and early diagnosis of asymptomatic breast carcinoma are considered good prognostic factors<sup>57</sup>. Carcinomas manifesting during pregnancy or lactation are poor prognostic with lower expression of hormonal receptors and high expression of HER 2/neu. Oral contraceptive does not bear any prognostic relationship<sup>58,59</sup>. Size of the tumor remains one of the strongest predictors of dissemination and rate of relapse in node negative disease. "Minimal breast cancer" includes all types of in-situ carcinomas together with invasive carcinomas with maximum

diameter of 1cm on subserial slicing of whole breast and mammography. It is recommended that the size of tumor should be measured to the nearest millimeter in fresh state and after fixation. On histologic section of the tumors measuring up to 1cm and/ or with in-situ component, the stage micrometer should be used<sup>60</sup>. Multicentric tumors are poor prognostic diseases. Chances of involvement of contra lateral breast are five times in patients suffering with carcinoma of one breast as compared to general population<sup>61</sup>.

Histologically, tubular, cribriform, mucinous and tubuloalveolar carcinomas are included in the excellent prognostic group; where as tubular mixed, mixed ductal NST, and classical lobular carcinomas are good prognostic. The average prognostic group includes mixed lobular, medullary and atypical medullary carcinomas and the poor prognostic group; ductal NST, mixed ductal and lobular and solid lobular carcinomas. Signet ring cell carcinomas and the ones clinically manifesting as inflammatory carcinomas have extremely bad prognosis. Squamous cell carcinoma, metaplastic carcinoma and carcinoma with neuroendocrine differentiation are said to be aggressive neoplasm but with little difference from IDC in survival rate<sup>62</sup>. A number of grading systems have been devised to correlate morphology with prognosis. With all grading systems, wide sampling is important because grading may vary in different areas and there may be mixing of patterns. The most widely used grading method for breast cancer is *Bloom Richardson system modified by Elliston and Ellis*, conceived for invasive ductal carcinoma. It can be applied to its special types and lobular carcinoma as well. In

this scheme, the grade is obtained by adding up the score of tubule formation, nuclear pleomorphism and mitotic count. Each is assigned a score from 1-3 points. The tumor is graded as- Grade 1(3-5 points); Grade 2(6-7 points); and Grade 3(8-9 points)<sup>63</sup>.

Extensive necrosis and inflammatory reaction at the periphery of the tumor (except in medullary carcinoma) may be associated with an increased incidence of lymph node metastasis and decreased survival rate. Stromal fibrosis and periductal and diffuse elastosis have not been found prognostic factors independent of histological type of tumor<sup>64-66</sup>. Assessment of in-situ component, particularly at the excision margin of the specimen removed for IDC, is becoming important in the context of conservative breast surgery. Extensive in-situ component left behind, may be the source of relapse<sup>67</sup>.

Careful examination of lymph nodes submitted from axillary chain, internal mammary chain (for medially located tumor) and sentinel lymph nodes is of critical importance. Lymph nodes measuring less than 5 mm may be processed in groups, sliced at two levels. Larger nodes should be sliced at right angles to long axis with a maximum of four lymph nodes per block. Immunostaining should be carried out in negative nodes with suspicious morphology. Over all, ten-year survival is reduced from 75% for node negative patients to 25-35% for nodes positive patients. The lymph node stage has been divided into three categories, stage A- no lymph node involvement; stage B- upto 3 axillary or single internal mammary node and stage C- 4 or more axillary nodes. Extracapsular infiltration of the nodal metastasis is poor prognostic and may warrant postoperative axillary

radiation<sup>68</sup>. Lymphovascular invasion should be called positive only when tumor cells are present in spaces having a clear lining of endothelial cells in the tissue adjoining the tumor and not within. Vascular invasion is one of the most important predictors of recurrences following conservative surgery and in flaps following mastectomy<sup>69</sup>.

The three most powerful prognostic determinants: lymph node stage, tumor size and histologic grade have been taken into consideration for calculating **Nottingham's Prognostic Index (NPI)**.

$$NPI-[size(cm) \times 0.2]+[lymph\ node\ stage(1-3)]+[grade(1-3)]$$

Score of less than 3.4 is good prognostic with 15 years survival compared to an age matched control population being 80%; score of 3.4-5.4, moderate group with 15 years survival 42% and score over 5.4, poor group with 15 years survival of 13%<sup>68</sup>.

Molecular prognostic/ predictive factors in use include hormone receptors, HER2/neu (c-erbB2). Immunohistochemistry, although less readily quantifiable, has substituted biochemical assay on fresh tumor tissue for estrogen/progesterone receptors (ER/PR) analysis; as the former can be carried out on small samples including fine needle aspirates and avoids sampling error. An attempt has been made to calculate a score (H-score) taking in to consideration number of the tumor cell nuclei stained and intensity of reaction; each assigned grade 0-4. Adding up the two scores, the scoring of two or less may be considered ER/PR negative with negligible chance of response to adjuvant hormone therapy<sup>70</sup>.

Hormone receptors positivity bears poor correlation with cytoarchitectural type; however the correlation of the receptors has been found lower in the tumors from premenopausal group compared to postmenopausal women. Estrogen receptors positivity correlates significantly with high nuclear and low histologic grades, absence of tumor necrosis, presence of marked tumor elastosis, older patient age group, absence of p53 mutation and absence of epidermal growth factor receptors<sup>70</sup>.

HER-2/neu is an oncogene that encodes a transmembrane glycoprotein with tyrosine kinase activity known as p185, which belongs to the family of growth factor receptors. Its overexpression can be measured by immunochemistry or FISH technique. It's over expression correlates with Herceptin therapy but is not good predictor of response to chemotherapy or survival rates<sup>71</sup>.

#### Future predictive markers

It is widely accepted that tumors, with a very high proliferation rate, such as acute leukemias, high grade lymphomas and germ cell tumors, can respond dramatically to chemotherapy. Similar, though less dramatic behaviour, has been reported in breast cancers. Thus parameters of cell proliferation activity and DNA ploidy, whether measured by old fashioned mitotic count, by MIB-1 (ki-67) or analog immunostain or determination of S phase fraction by flow cytometry have emerged as very important prognostic determinants. In one study tumor with a low S phase fraction (SPF < 5%) had a response rate of 46% and with an intermediate SPF (5-10%) of 84%. All patients with a high SPF (> 10%) responded to chemotherapy<sup>72</sup>. Presence of predictors of invasion and metastasis at the

advancing edge of tumor has a bearing on the invasive and metastatic ability of the tumor. Elevated levels of plasminogen activators and inhibitors, such as urokinase type plasminogen activator (uPA) and plasminogen activator inhibitor 1(PAI-1), are independent predictors of shortened relapse free survival and over all survival. Patients with uPA negative tumors have a better response to tamoxifen treatment than those with uPA positive tumors<sup>73</sup>. Cathepsin D is a lysosomal protein that is likely to have a role in tumor invasion and metastasis. The level of cathepsin D in normal breast is lower than 8 units/dl. This protease is overexpressed and secreted by breast cancer cells. In node negative patients, cathepsin D overexpression has been shown to be an important predictor of poor survival and recurrences<sup>74</sup>. Over expression of cell cycle regulator, cyclinD1 (required for transition from G1 to S phase of cycle) has not been found an independent prognostic marker in breast cancer<sup>75</sup>. P53 gene is involved in the control of cell growth by keeping a check on the entry of cell into S phase. Mutation in p53 gene correlates with aneuploidy, absence of hormone receptors, a high tumor grade, a high S phase fraction, postmenopausal status and reduced patient survival<sup>76</sup>. The nm23 gene has been associated with metastatic suppressive ability. In breast cancer, reduced nm23H-1 expression correlates with high metastatic potential<sup>77</sup>.

E-cadherin and its down stream molecular alpha catenin are involved in hemotypic cell interactors. Loss of expression of these molecules correlates with metastasis<sup>78</sup>. A gain in expression of alpha-6-integrin is associated with reduced survival, which facilitates the adhesion of tumor cells to the vascular

endothelium. CD44 is a transmembrane glycoprotein occurring in several isoforms. In breast cancer, expression of CD44V6 has been shown to be independent predictor of overall poor survival<sup>80</sup>. Expression of vascular endothelial factor (VEGF) and platelet derived growth factor (PDGF) as studied by immunostain and RT-PCR methods, correlates with microvessel counts or tumor angiogenesis. This is a potent and independent prognostic indicator, especially in early stage of cancer<sup>81</sup>.

### Genetic predisposition

Identification of breast cancer susceptibility genes namely- BRCA-1 and BRCA-2 and ATM has revolutionized the breast cancer research. BRCA-1 is a tumor suppressor gene and women with mutation in this gene are at high risk of developing early onset breast and ovarian cancers. Genetic mutations are inherited in an autosomal dominant manner and mutations in BRCA-1 account for 50% of inherited breast cancer. The other gene associated with familial early onset breast cancer is BRCA-2 localized on chromosome 13q12-13. About 70% of breast cancer families, which do not harbour mutation in BRCA-1, have mutations in BRCA-2 gene. Patients of ataxia-telengectasia (homozygous state) carry a risk of cancer 60-180 times above general population<sup>82</sup>. There are great hopes that evaluation of expression of thousands of genes through microarray technology, that allows a much sharper separation of prognostic groups than is currently possible, and markers of response to specific treatment, will be identified so that patients can get the most suitable treatment for the individual tumor without delay.

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### Know about CSF

**F**ormation 0.5ml/min. 60% by choroid plexus in lateral ventricles and 40% by exposed vessels on verthicular walls.

#### Composition:

150 ml (Roughly)  
Clear, colourless  
No red blood cells  
Proteins 20 mg%  
Glucose 50% of Plasma

Calcium, cholestrol, urea are lower than plasma. Chloride, creatinine are higher than plasma.

Pressure : 10-13 cm of water

Functions supports brain tissue  
Regulates brain ECF Provides Protein transport

#### Foot

- 26 Bones
- 29 Joints
- 42 Intrinsic muscles
- Numerous ligaments
- Increased vascularity

Human being walks 4,500-6,000 steps per day, on an average. He/she walks 1,85,000 km in his/her life time which amounts to going through the world four times.

= Diabetic Foot

In diabetic foot the rule of 15 is as follows:

15% of diabetic patients have foot problems

of these 15% are diagnosed

of these 15% are treated

of these 15% are amputed

## Guidelines for the Contributors

**Submission of manuscript:** All manuscripts submitted for publication to the NBE Journal of Post graduate Medical Education, Training & Research should include the following:

**1. Covering letter:** One of the authors could be identified as the corresponding author of the paper, who would be responsible for the correspondence with the editor.

**2. Manuscript:** Manuscripts can be submitted in a CD (compact disc) in MS Word (in addition to one hard copy). Typescript should be sent to the Editor, NBE Journal of Post graduate Medical Education, Training & Research, National Board of Examinations, Ring Road, Ansari Nagar, New Delhi- 110 029 (India).

Manuscripts should be presented in as concise a form as possible, typewritten in double space on one side of a good quality bond paper (21.0 x 29.7 cms). Pages should be numbered consecutively and the contents arranged in the following order:- Title; Name(s) of the author(s); Department(s) and Institution (s); Abstract; Key words; Introduction; Material & Methods; Results; Discussion; Acknowledgement; and References. Abstract, Tables and Legends for Figures should be typed on separate sheets and not in continuation of the main text.

**Title:** Title of the article should be short, continuous (broken or hyphenated titles are not acceptable) and yet sufficiently descriptive and informative so as to be useful in indexing and information retrieval.

**Abstract:** Abstract should be brief (250 words) and indicate the scope and significant results of the paper. It should only highlight the principal findings and conclusions so that it can be used by abstracting services without modification. Conclusions and recommendations not found in the text of the articles should not be inserted in the Abstract. A set of suitable key words arranged alphabetically may be provided.

**Introduction:** Introduction should be brief and state precisely the scope of the paper. Review of the literature should be restricted to reasons for undertaking the present study and provide only the most essentials background. This should cover the study area, study population, sample size, sampling techniques and the data collection techniques and tools, data analyses and statistical analyses.

**Results:** Only such data as are essential for understanding the discussion and main conclusions emerging from the study should be included. The data should be arranged in unified and coherent sequence. Data presented in tables and figures should not be repeated in the text. Only important observations need to be emphasized or summarised.

**Discussion:** The discussion should deal with the interpretation of results without repeating information already presented under Results. It should relate new findings to the known ones and include logical deductions. It should also mention any weaknesses of the study. The conclusions can be linked with the goals of the study. All hypotheses should, if warranted, clearly be identified as such; recommendations may be included as part of Discussion, only when considered absolutely necessary and relevant.

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2. Books and Monograph- Murray RR, Ruesenthal KS. Medical Microbiology. 4th ed. St. Louis: Mosby; 2002.
3. Chapter in a book- Meltzen PS, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, editor. The Genetic basis of human cancer, Newyork: MC GrawHill; 2002. p. 93-113
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6. Internet article- Abood S. Quality improvement initiatives in running homes Am J Nurs, 2002 Jun; 102 (6), available from: <http://www.muningworld.org/AJN/2002.nurseswatch.com>

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